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(54) Title: METHOD OF USING A MATRIX METALLOPROTEINASE INHIBITOR AND RADIATION THERAPY AS COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA

(57) Abstract

The present invention provides methods to treat neoplasia disorders in a mammal using a combination of radiation and a matrix metalloproteinase inhibitor.

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METHOD OF USING A MATRIX METALLAPROTEINASE INHIBITOR AND RADIATION THERAPY AS COMBINATION THERAPY IN THE TREATMENT OF NEOPLASIA

Field of the Invention

The present invention relates to a combination of radiation therapy and a matrix metalloproteinase (MMP) inhibitor for treatment of neoplasia disorders. More specifically, this invention relates to the use of MMP inhibitors in combination with radiation therapy for treating cancer.

Background of the Invention

A neoplasm, or tumor, is an abnormal, unregulated, and disorganized proliferation of cell growth. A neoplasm is malignant, or cancerous, if it has properties of destructive growth, invasiveness and metastasis. Invasiveness refers to the local spread of a neoplasm by infiltration or destruction of surrounding tissue, typically breaking through the basal laminas that define the boundaries of the tissues, thereby often entering the body's circulatory system. Metastasis typically refers to the dissemination of tumor cells by lymphatics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance.

Cancer is now the second leading cause of death in the United States and over 8,000,000 persons in the United States have been diagnosed with cancer. In 1995,

cancer accounted for 23.3% of all deaths in the United States.

Cancer is not fully understood on the molecular level. It is known that exposure of a cell to a carcinogen such as certain viruses, certain chemicals, or radiation, leads to DNA alteration that inactivates a "suppressive" gene or activates an "oncogene". Suppressive genes are growth regulatory genes, which upon mutation, can no longer control cell growth. Oncogenes are initially normal genes (called proto-oncogenes) that by mutation or altered context of expression become transforming genes. The products of transforming genes cause inappropriate cell growth. More than twenty different normal cellular genes can become oncogenes by genetic alteration. Transformed cells differ from normal cells in many ways, including cell morphology, cell-to-cell interactions, membrane content, cytoskeletal structure, protein secretion, gene expression and mortality.

Cancer is now primarily treated with one or a combination of three types of therapies: surgery, radiation, and chemotherapy. Surgery involves the bulk removal of diseased tissue. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, and skin, it cannot be used in the treatment of tumors located in other areas, inaccessible to surgeons, nor in the treatment of disseminated neoplastic conditions such as leukemia.

Chemotherapy involves the disruption of cell replication or cell metabolism. It is used most often in the treatment of breast, lung, and testicular cancer.

The adverse effects of systemic chemotherapy used in the treatment of neoplastic disease is most feared by patients undergoing treatment for cancer. Of these adverse effects nausea and vomiting are the most common and severe side effects. Other adverse side effects include cytopenia, infection, cachexia, mucositis in patients receiving high doses of chemotherapy with bone marrow rescue or radiation therapy; alopecia (hair loss); cutaneous complications such as pruritis, urticaria, and angioedema; neurological complications; pulmonary and cardiac complications in patients receiving radiation or chemotherapy; and reproductive and endocrine complications (M. Abeloff, et al., Alopecia and Cutaneous Complications, in Clinical Oncology 755-56 (Abeloff, ed. 1992).

Chemotherapy-induced side effects significantly impact the quality of life of the patient and may dramatically influence patient compliance with treatment.

Additionally, adverse side effects associated with chemotherapeutic agents are generally the major dose-limiting toxicity (DLT) in the administration of these drugs. For example, mucositis, is one of the major dose limiting toxicity for several anticancer agents, including the antimetabolite cytotoxic agents 5-FU, methotrexate, and antitumor antibiotics, such as doxorubicin. Many of these chemotherapy-induced side effects if severe, may lead to hospitalization, or require treatment with analgesics for the treatment of pain.

In general, radiation therapy is employed as potentially curative therapy for patients who present

with clinically localized disease and are expected to live at least 10 years.

For example, approximately 70% of newly diagnosed prostate cancer patients fall into this category. Approximately 10% of these patients (7% of total patients) undergo radiation therapy. Approximately 80% of patients who have undergone radiation as their primary therapy have disease persistence or develop recurrence or metastasis within five years after treatment. Currently, most of these radiotherapy patients generally do not receive any immediate follow-up therapy. Rather, they are monitored frequently, such as for elevated Prostate Specific Antigen ("PSA"), which is the primary indicator of recurrence or metastasis in prostate cancer.

The adverse side effects induced by chemotherapeutic agents and radiation therapy have become of major importance to the clinical management of cancer patients.

Colorectal Cancer

Survival from colorectal cancer depends on the stage and grade of the tumor, for example precursor adenomas to metastatic adenocarcinoma. Generally, colorectal cancer can be treated by surgically removing the tumor, but overall survival rates remain between 45 and 60 percent. Colonic excision morbidity rates are fairly low and is generally associated with the anastomosis and not the extent of the removal of the tumor and local tissue. In patients with a high risk of reoccurrence, however, chemotherapy has been incorporated into the treatment regimen in order to improve survival rates.

Tumor metastasis prior to surgery is generally believed to be the cause of surgical intervention failure and up to one year of chemotherapy is required to kill the non-excised tumor cells. As severe toxicity is associated with the chemotherapeutic agents, only patients at high risk of recurrence are placed on chemotherapy following surgery.

Prostate Cancer

Prostate cancer is now the leading form of cancer among men and the second most frequent cause of death from cancer in men. It is estimated that more than 165,000 new cases of prostate cancer were diagnosed in 1993, and more than 35,000 men died from prostate cancer in that year. Additionally, the incidence of prostate cancer has increased by 50% since 1981, and mortality from this disease has continued to increase. Previously, most men died of other illnesses or diseases before dying from their prostate cancer. We now face increasing morbidity from prostate cancer as men live longer and the disease has the opportunity to progress.

Current therapies for prostate cancer focus upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. Radiation alone or in combination with surgery and/or chemotherapeutic agents is often used.

In addition to the use of digital rectal examination and transrectal ultrasonography, prostate-specific antigen (PSA) concentration is frequently used in the diagnosis of prostate cancer.

U.S. Pat. No. 4,472,382 discloses treatment of benign prostatic hyperplasia (BPH) with an antiandrogen and certain peptides which act as LH-RH agonists. U.S.

Pat. No. 4,596,797 discloses aromatase inhibitors as a method of prophylaxis and/or treatment of prostatic hyperplasia. U.S. Pat. No. 4,760,053 describes a treatment of certain cancers which combines an LHRH agonist with an antiandrogen and/or an antiestrogen and/or at least one inhibitor of sex steroid biosynthesis. U.S. Pat. No. 4,775,660 discloses a method of treating breast cancer with a combination therapy which may include surgical or chemical prevention of ovarian secretions and administering an antiandrogen and an antiestrogen. U.S. Pat. No. 4,659,695 discloses a method of treatment of prostate cancer in susceptible male animals including humans whose testicular hormonal secretions are blocked by surgical or chemical means, e.g. by use of an LHRH agonist, which comprises administering an antiandrogen, e.g. flutamide, in association with at least one inhibitor of sex steroid biosynthesis, e.g. aminoglutethimide and/or ketoconazole.

Prostate Specific Antigen

One well known prostate cancer marker is Prostate Specific Antigen (PSA). PSA is a protein produced by prostate cells and is frequently present at elevated levels in the blood of men who have prostate cancer. PSA has been shown to correlate with tumor burden, serve as an indicator of metastatic involvement, and provide a parameter for following the response to surgery, irradiation, and androgen replacement therapy in prostate cancer patients. It should be noted that Prostate Specific Antigen (PSA) is a completely different protein from Prostate Specific Membrane Antigen (PSMA). The two proteins have different

structures and functions and should not be confused because of their similar nomenclature.

Prostate Specific Membrane Antigen (PSMA)

In 1993, the molecular cloning of a prostate-specific membrane antigen (PSMA) was reported as a potential prostate carcinoma marker and hypothesized to serve as a target for imaging and cytotoxic treatment modalities for prostate cancer. Antibodies against PSMA have been described and examined clinically for diagnosis and treatment of prostate cancer. In particular, Indium-111 labeled PSMA antibodies have been described and examined for diagnosis of prostate cancer and indium-labeled PSMA antibodies have been described and examined for the treatment of prostate cancer.

Pancreas Cancer

Approximately 2% of new cancer cases diagnoses in the United States is pancreatic cancer. Pancreatic cancer is generally classified into two clinical types: 1) adenocarcinoma (metastatic and non-metastatic), and 2) cystic neoplasms (serous cystadenomas, mucinous cystic neoplasms, papilary cystic neoplasms, acinar cell systadenocarcinoma, cystic choriocarcinoma, cystic teratomas, angiomatous neoplasms).

Ovary Cancer

Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. Preferred single agents that can be used in combination include: alkylating agents, ifosfamide, cisplatin, carboplatin, taxol, doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha and interferon gamma.

Cancer of the fallopian tube is the least common type of ovarian cancer, accounting for approximately 400 new cancer cases per year in the United States. Papillary serous adenocarcinoma accounts for approximately 90% of all malignancies of the ovarian tube.

Detailed Description of the Invention

Treatment of a neoplasia disorder in a mammal in need of such treatment is provided by methods and combinations using radiation and a MMP inhibitor. The method comprises treating a mammal with a therapeutically effective amount of a combination comprising a MMP inhibitor and a radiotherapeutic agent. Besides being useful for human treatment, the present invention is also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

Inhibitors of MMP potentiate tumor response to radiation. Thus, MMP inhibitors improve the efficacy of radiotherapy.

The methods and combinations of the present invention may be used for the treatment of neoplasia disorders selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choriod plexus papilloma/carcinoma,

clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiatied carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

The methods and compositions of the present invention provide one or more benefits. A combination of a MMP inhibitor with radiation therapy of the present invention are useful in treating neoplasia disorders. Preferably, the MMP inhibitor agent or agents and the

radiation therapies of the present invention is administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations for each of the individual components administered alone.

A benefit of lowering the dose of the radiation therapies of the present invention administered to a mammal includes a decrease in the incidence of adverse effects associated with higher dosages.

By lowering the incidence of adverse effects, an improvement in the quality of life of a patient undergoing treatment for cancer is contemplated. Further benefits of lowering the incidence of adverse effects include an improvement in patient compliance, and a reduction in the number of hospitalizations needed for the treatment of adverse effects.

Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine,

chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

Also included in the combination of the invention are the isomeric forms and tautomers of the described compounds and the pharmaceutically-acceptable salts thereof. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other

physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

A MMP inhibitor of the present invention can be formulated as a pharmaceutical composition. Such a composition can then be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania; 1975 and Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable

dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Dimethyl acetamide, surfactants including ionic and non-ionic detergents, polyethylene glycols can be used. Mixtures of solvents and wetting agents such as those discussed above are also useful.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter, synthetic mono- di- or triglycerides, fatty acids and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration can include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, a contemplated aromatic sulfone hydroximate inhibitor compound can be admixed with lactose, sucrose, starch powder, cellulose

esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation as can be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents such as sodium citrate, magnesium or calcium carbonate or bicarbonate. Tablets and pills can additionally be prepared with enteric coatings.

For therapeutic purposes, formulations for parenteral administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. A contemplated MMP inhibitor compound can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as

wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form varies depending upon the mammalian host treated and the particular mode of administration.

The term "treatment" refers to any process, action, application, therapy, or the like, wherein a mammal, including a human being, is subject to medical aid with the object of improving the mammal's condition, directly or indirectly.

The term "inhibition," in the context of neoplasia, tumor growth or tumor cell growth, may be assessed by delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, among others. In the extreme, complete inhibition, is referred to herein as prevention.

The phrase "combination therapy" (or "co-therapy") embraces the administration of a matrix metalloproteinase inhibitor and radiation therapy, and, optionally, an antineoplastic agent, as part of a specific treatment regimen intended to provide a beneficial effect from the co-action of the matrix metalloproteinase inhibitor and the radiation therapy. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of the matrix metalloproteinase inhibitor and the radiation therapy. Administration of the matrix metalloproteinase inhibitor

and the radiation therapy in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" generally is not intended to encompass the administration of a matrix metalloproteinase inhibitor and radiation therapy as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy" is intended to embrace administration of a matrix metalloproteinase inhibitor and radiation therapy in a sequential manner, that is, wherein the matrix metalloproteinase inhibitor and the radiation therapy are administered at different times, as well as administration of the matrix metalloproteinase and radiation therapy in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject concurrently with radiation therapy a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each therapeutic agent. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents, if more than one, can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively,

for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the matrix metalloproteinase inhibitor and radiation therapy are administered is not narrowly critical although radiation therapy typically will follow the administration of the matrix metalloproteinase inhibitor. "Combination therapy" also can embrace the administration of the matrix metalloproteinase inhibitor and radiation therapy as described above in further combination with other biologically active ingredients (such as, but not limited to, an antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery). The radiation treatment of the combination may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the matrix metalloproteinase inhibitor and radiation treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved even when the radiation treatment is temporally removed from the administration of the matrix metalloproteinase inhibitor, perhaps by days or even weeks.

The term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia.

Angiogenesis is an attractive therapeutic target because it is a multi-step process that occurs in a specific sequence, thus providing several possible targets for drug action. Examples of agents that interfere with several of these steps include specific MMP inhibitors.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent that will achieve the goal of improvement in neoplastic disease severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

A "therapeutic effect" relieves to some extent one or more of the symptoms of a neoplasia disorder. In reference to the treatment of a cancer, a therapeutic effect refers to one or more of the following: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 4) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 5) inhibition, to some extent, of tumor growth; 6) relieving or reducing to some extent one or more of the symptoms associated with the disorder; and/or 7) relieving or reducing the side effects associated with the administration of anticancer agents.

"Therapeutic effective amount" is intended to qualify the amount required to achieve a therapeutic effect.

The phrases "low dose" or "low dose amount", in characterizing a therapeutically effective amount of the MMP inhibitor and the radiation or therapy in the

combination therapy, defines a quantity of such therapy, or a range of quantity of such therapy, that is capable of diminishing the neoplastic disease while reducing or avoiding one or more radiation-induced side effects, such as myelosupression, cardiac toxicity, skin erythema and desquamation, alopecia, inflammation or fibrosis.

The phrase "adjunctive therapy" includes agents such as those, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents; prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation; or reduce the incidence of infection associated with the administration of myelosuppressive anticancer drugs.

The phrase a "radiotherapeutic agent" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia. Examples of radiotherapeutic agents are provided in, but not limited to, radiation therapy and is known in the art (Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, 248-75 (Devita et al., ed., 4th edit., volume 1, 1993).

The term "clinical tumor" includes neoplasms that are identifiable through clinical screening or diagnostic procedures including, but not limited to, palpation, biopsy, cell proliferation index, endoscopy, mammography, digital mammography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), radiography, radionuclide evaluation, CT- or MRI-guided aspiration cytology, and imaging-guided needle biopsy, among others. Such diagnostic techniques are well known to

those skilled in the art and are described in Cancer Medicine 4th Edition, Volume One. J.F. Holland, R.C. Bast, D.L. Morton, E. Frei III, D.W. Kufe, and R.R. Weichselbaum (Editors). Williams & Wilkins, Baltimore (1997).

The term "tumor marker" or "tumor biomarker" encompasses a wide variety of molecules with divergent characteristics that appear in body fluids or tissue in association with a clinical tumor and also includes tumor-associated chromosomal changes. Tumor markers fall primarily into three categories: molecular or cellular markers, chromosomal markers, and serological or serum markers. Molecular and chromosomal markers complement standard parameters used to describe a tumor (i.e. histopathology, grade, tumor size) and are used primarily in refining disease diagnosis and prognosis after clinical manifestation. Serum markers can often be measured many months before clinical tumor detection and are thus useful as an early diagnostic test, in patient monitoring, and in therapy evaluation.

Molecular Tumor Markers

Molecular markers of cancer are products of cancer cells or molecular changes that take place in cells because of activation of cell division or inhibition of apoptosis. Expression of these markers can predict a cell's malignant potential. Because cellular markers are not secreted, tumor tissue samples are generally required for their detection. Non-limiting examples of molecular tumor markers that can be used in the present invention are listed in Table No. 1, below.

Table No. 1. Non-limiting Examples of Molecular Tumor Markers

Tumor	Marker
Breast	p53
Breast, Ovarian	ErbB-2/Her-2
Breast	S phase and ploidy
Breast	pS2
Breast	MDR2
Breast	urokinase plasminogen activator
Breast, Colon, Lung	*myc* family

Chromosomal Tumor Markers

Somatic mutations and chromosomal aberrations have been associated with a variety of tumors. Since the identification of the Philadelphia Chromosome by Nowel and Hungerford, a wide effort to identify tumor-specific chromosomal alterations has ensued. Chromosomal cancer markers, like cellular markers, are can be used in the diagnosis and prognosis of cancer. In addition to the diagnostic and prognostic implications of chromosomal alterations, it is hypothesized that germ-line mutations can be used to predict the likelihood that a particular person will develop a given type of tumor. Non-limiting examples of chromosomal tumor markers that can be used in the present invention are listed in Table No. 2, below.

Table No. 2. Non-limiting Examples of Chromosomal Tumor Markers

Tumor	Marker
Breast	1p36 loss

Breast	6q24-27 loss
Breast	11q22-23 loss
Breast	11q13 amplification
Breast	*TP53* mutation
Colon	Gain of chromosome 13
Colon	Deletion of short arm of chromosome 1
Lung	Loss of 3p
Lung	Loss of 13q
Lung	Loss of 17p
Lung	Loss of 9p

Serological Tumor Markers

Serum markers including soluble antigens, enzymes and hormones comprise a third category of tumor markers. Monitoring serum tumor marker concentrations during therapy provides an early indication of tumor recurrence and of therapy efficacy. Serum markers are advantageous for patient surveillance compared to chromosomal and cellular markers because serum samples are more easily obtainable than tissue samples,. and because serum assays can be performed serially and more rapidly. Serum tumor markers can be used to determine appropriate therapeutic doses within individual patients. For example, the efficacy of a combination regimen consisting of chemotherapeutic and antiangiogenic agents can be measured by monitoring the relevant serum cancer marker levels. Moreover, an efficacious therapy dose can be achieved by modulating the therapeutic dose so as to keep the particular serum tumor marker concentration stable or within the reference range, which may vary depending upon the indication. The amount of therapy

can then be modulated specifically for each patient so as to minimize side effects while still maintaining stable, reference range tumor marker levels. Table No. 3 provides non-limiting examples of serological tumor markers that can be used in the present invention.

Table No. 3. Non-limiting Examples of Serum Tumor Markers

Cancer Type	**Marker**
Germ Cell Tumors	a-fetoprotein (AFP)
Germ Cell Tumors	human chorionic gonadotrophin (hCG)
Germ Cell Tumors	placental alkaline phosphatase (PLAP)
Germ Cell Tumors	lactate dehydrogenase (LDH)
Prostate	prostate specific antigen (PSA)
Breast	carcinoembryonic antigen (CEA)
Breast	MUC-1 antigen (CA15-3)
Breast	tissue polypeptide antigen (TPA)
Breast	tissue polypeptide specific antigen (TPS)
Breast	CYFRA 21.1
Breast	soluble *erb*-B-2
Ovarian	CA125
Ovarian	OVX1
Ovarian	cancer antigen CA72-4
Ovarian	TPA

Ovarian	TPS
Gastrointestinal	CD44v6
Gastrointestinal	CEA
Gastrointestinal	cancer antigen CA19-9
Gastrointestinal	NCC-ST-439 antigen (Dukes C)
Gastrointestinal	cancer antigen CA242
Gastrointestinal	soluble *erb*-B-2
Gastrointestinal	cancer antigen CA195
Gastrointestinal	TPA
Gastrointestinal	YKL-40
Gastrointestinal	TPS
Esophageal	CYFRA 21-1
Esophageal	TPA
Esophageal	TPS
Esophageal	cancer antigen CA19-9
Gastric Cancer	CEA
Gastric Cancer	cancer antigen CA19-9
Gastric Cancer	cancer antigen CA72-4
Lung	neruon specific enolase (NSE)
Lung	CEA
\Lung	CYFRA 21-1
Lung	cancer antigen CA 125
Lung	TPA
Lung	squamous cell carcinoma antigen (SCC)
Pancreatic cancer	ca19-9
Pancreatic cancer	ca50
Pancreatic cancer	ca119
Pancreatic cancer	ca125
Pancreatic cancer	CEA

Pancreatic cancer	
Renal Cancer	CD44v6
Renal Cancer	E-cadherin
Renal Cancer	PCNA (proliferating cell nuclear antigen)

Examples

Germ Cell Cancers

Non-limiting examples of tumor markers useful in the present invention for the detection of germ cell cancers include, but are not limited to, a-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and its beta subunit (hCGb), lactate dehydrogenase (LDH), and placental alkaline phosphatase (PLAP).

AFP has an upper reference limit of approximately -10 kU/L after the first year of life and may be elevated in germ cell tumors, hepatocellular carcinoma and also in gastric, colon, biliary, pancreatic and lung cancers. AFP serum half life is approximately five days after orchidectomy. According to EGTM recommendations, AFP serum levels less than 1,000 kU/L correlate with a good prognosis, AFP levels between 1,000 and 10,000 kU/L, inclusive, correlate with intermediate prognosis, and AFP levels greater than 10,000 U/L correlate with a poor prognosis.

HCG is synthesized in the placenta and is also produced by malignant cells. Serum hCG concentrations may be increased in pancreatic adenocarcinomas, islet cell tumors, tumors of the small and large bowel, hepatoma, stomach, lung, ovaries, breast and kidney. Because some tumors only hCGb, measurement of both hCG

and hCGb is recommended. Normally, serum hCG in men and pre-menopausal women is as high as -5 U/L while post-menopausal women have levels up to -10 U/L. Serum half life of hCG ranges from 16-24 hours. According to the EGTM, hCG serum levels under 5000 U/L correlate with a good prognosis, levels between 5000 and 50000 U/L, inclusively correlate with an intermediate prognosis, and hCG serum levels greater than 50000 U/L correlate with a poor prognosis. Further, normal hCG half lives correlate with good prognosis while prolonged half lives correlate with poor prognosis.

LDH is an enzyme expressed in cardiac and skeletal muscle as well as in other organs. The LDH-1 isoenzyme is most commonly found in testicular germ cell tumors but can also occur in a variety of benign conditions such as skeletal muscle disease and myocardial infarction. Total LDH is used to measure independent prognostic value in patients with advanced germ cell tumors. LDH levels less than 1.5 x the reference range are associated with a good prognosis, levels between 1.5 and 10 x the reference range, inclusive, are associated with an intermediate prognosis, and levels more than 10 x the reference range are associated with a poor prognosis.

PLAP is a enzyme of alkaline phosphatase normally expressed by placental syncytiotrophoblasts. Elevated serum concentrations of PLAP are found in seminomas, non-seminomatous tumors, and ovarian tumors, and may also provide a marker for testicular tumors. PLAP has a normal half life after surgical resection of between 0.6 and 2.8 days.

<u>Prostate Cancer</u>

A nonlimiting example of a tumor marker useful in the present invention for the detection of prostate cancer is prostate specific antigen (PSA). PSA is a glycoprotein that is almost exclusively produced in the prostate. In human serum, uncomplexed f-PSA and a complex of f-PSA with a1-anthichymotrypsin make up total PSA (t-PSA). T-PSA is useful in determining prognosis in patients that are not currently undergoing anti-androgen treatment. Rising t-PSA levels via serial measurement indicate the presence of residual disease.

Breast Cancer

Non-limiting examples of serum tumor markers useful in the present invention for the detection of breast cancer include, but is not limited to carcinoembryonic antigen (CEA) and MUC-1 (CA 15.3). Serum CEA and CA15.3 levels are elevated in patients with node involvement compared to patients without node involvement, and in patients with larger tumors compared to smaller tumors. Normal range cutoff points (upper limit) are 5-10 mg/L for CEA and 35-60 u/ml for CA15.3. Additional specificity (99.3%) is gained by confirming serum levels with two serial increases of more than 15%.

Ovarian Cancer

A non-limiting example of a tumor marker useful in the present invention for the detection of ovarian cancer is CA125. Normally, women have serum CA125 levels between 0-35 kU/L; 99% of post-menopausal women have levels below 20 kU/L. Serum concentration of CA125 after chemotherapy is a strong predictor of outcome as elevated CA125 levels are found in roughly 80% of all patients with epithelial ovarian cancer. Further, prolonged CA125 half-life or a less than 7-fold decrease

during early treatment is also a predictor of poor disease prognosis.

Gastrointestinal Cancers

A non-limiting example of a tumor marker useful in the present invention for the detection of colon cancer is carcinoembryonic antigen (CEA). CEA is a glycoprotein produced during embryonal and fetal development and has a high sensitivity for advanced carcinomas including those of the colon, breast, stomach and lung. High pre- or postoperative concentrations (>2.5 ng/ml) of CEA are associated with worse prognosis than are low concentrations. Further, some studies in the literature report that slow rising CEA levels indicates local recurrence while rapidly increasing levels suggests hepatic metastasis.

Lung Cancer

Examples of serum markers useful in the present invention to monitor lung cancer therapy include, but are not limited to, CEA, cytokeratin 19 fragments (CYFRA 21-1), and Neuron Specific Enolase (NSE).

NSE is a glycolytic isoenzyme of enolase produced in central and peripheral neurons and malignant tumors of neuroectodermal origin. At diagnosis, NSE concentrations greater than 25 ng/mL are suggestive of malignancy and lung cancer while concentrations greater than 100 ng/mL are suggestive of small cell lung cancer.

CYFRA 21-1 is a tumor marker test which uses two specific monoclonal antibodies against a cytokeratin 19 fragment. At diagnosis, CYFRA 21-1 concentrations greater than 10 ng/mL are suggestive of malignancy while concentrations greater than 30 ng/mL are suggestive of lung cancer.

Accordingly, dosing of the matrix metalloproteinase inhibitor and radiation therapy may be determined and adjusted based on measurement of tumor markers in body fluids or tissues, particularly based on tumor markers in serum. For example, a decrease in serum marker level relative to baseline serum marker prior to administration of the matrix metalloproteinase inhibitor and radiation therapy indicates a decrease in cancer-associated changes and provides a correlation with inhibition of the cancer. In one embodiment, therefore, the method of the present invention comprises administering the matrix metalloproteinase inhibitor and radiation therapy at doses that in combination result in a decrease in one or more tumor markers, particularly a decrease in one or more serum tumor markers, in the mammal relative to baseline tumor marker levels.

Similarly, decreasing tumor marker concentrations or serum half lives after administration of the combination indicates a good prognosis, while tumor marker concentrations which decline slowly and do not reach the normal reference range predict residual tumor and poor prognosis. Further, during follow-up therapy, increases in tumor marker concentration predicts recurrent disease many months before clinical manifestation.

In addition to the above examples, Table No. 4, below, lists several references, hereby individually incorporated by reference herein, that describe tumor markers and their use in detecting and monitoring tumor growth and progression.

Table No. 4. Tumor marker references.

European Group on Tumor Markers Publications Committee. Consensus Recommendations. Anticancer Research *19*: 2785-2820 (1999)
Human Cytogenetic Cancer Markers. Sandra R. Wolman and Stewart Sell (eds.). Totowa, New Jersey: Humana Press. 1997
Cellular Markers of Cancer. Carleton Garrett and Stewart Sell (eds.). Totowa, New Jersey: Human Press. 1995

The phrase "matrix metalloproteinase inhibitor" or "MMP inhibitor" includes agents that specifically inhibit a class of enzymes, the zinc metalloproteinases (metalloproteases). The zinc metalloproteinases are involved in the degradation of connective tissue or connective tissue components. These enzymes are released from resident tissue cells and/or invading inflammatory or tumor cells. Blocking the action of zinc metalloproteinases interferes with the creation of paths for newly forming blood vessels to follow. Examples of MMP inhibitors are described in Golub, LM, Inhibition of Matrix Metalloproteinases: Therapeutic Applications (Annals of the New York Academy of Science, Vol 878). Robert A. Greenwald and Stanley Zucker (Eds.), June 1999), and is hereby incorporated by reference.

Connective tissue, extracellular matrix constituents and basement membranes are required components of all mammals. These components are the biological materials that provide rigidity, differentiation, attachments and, in some cases, elasticity to biological systems including human beings and other mammals. Connective tissues components include, for example, collagen, elastin, proteoglycans, fibronectin and laminin. These biochemicals makeup, or are components of structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea and vitreous humor.

Under normal conditions, connective tissue turnover and/or repair processes are controlled and in equilibrium. The loss of this balance for whatever reason leads to a number of disease states. Inhibition of the enzymes responsible loss of equilibrium provides

a control mechanism for this tissue decomposition and, therefore, a treatment for these diseases.

Degradation of connective tissue or connective tissue components is carried out by the action of proteinase enzymes released from resident tissue cells and/or invading inflammatory or tumor cells. A major class of enzymes involved in this function are the zinc metalloproteinases (metalloproteases).

The metalloprotease enzymes are divided into classes with some members having several different names in common use. Examples are: collagenase I (MMP-1, fibroblast collagenase; EC 3.4.24.3); collagenase II (MMP-8, neutrophil collagenase; EC 3.4.24.34), collagenase III (MMP-13), stromelysin 1 (MMP-3; EC 3.4.24.17), stromelysin 2 (MMP-10; EC 3.4.24.22), proteoglycanase, matrilysin (MMP-7), gelatinase A (MMP-2, 72kDa gelatinase, basement membrane collagenase; EC 3.4.24.24), gelatinase B (MMP-9, 92kDa gelatinase; EC 3.4.24.35), stromelysin 3 (MMP-11), metalloelastase (MMP-12, HME, human macrophage elastase) and membrane MMP (MMP-14). MMP is an abbreviation or acronym representing the term Matrix Metalloprotease with the attached numerals providing differentiation between specific members of the MMP group.

The uncontrolled breakdown of connective tissue by metalloproteases is a feature of many pathological conditions. Examples include rheumatoid arthritis, osteoarthritis, septic arthritis; corneal, epidermal or gastric ulceration; tumor metastasis, invasion or angiogenesis; periodontal disease; proteinuria; Alzheimer's Disease; coronary thrombosis and bone disease. Defective injury repair processes also occur.

This can produce improper wound healing leading to weak repairs, adhesions and scarring. These latter defects can lead to disfigurement and/or permanent disabilities as with post-surgical adhesions.

Matrix metalloproteases are also involved in the biosynthesis of tumor necrosis factor (TNF) and inhibition of the production or action of TNF and related compounds is an important clinical disease treatment mechanism. TNF-α, for example, is a cytokine that at present is thought to be produced initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large integer of deleterious effects *in vitro* and *in vivo*. For example, TNF can cause and/or contribute to the effects of inflammation, rheumatoid arthritis, autoimmune disease, multiple sclerosis, graft rejection, fibrotic disease, cancer, infectious diseases, malaria, mycobacterial infection, meningitis, fever, psoriasis, cardiovascular/pulmonary effects such as post-ischemic reperfusion injury, congestive heart failure, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage and acute phase responses like those seen with infections and sepsis and during shock such as septic shock and hemodynamic shock. Chronic release of active TNF can cause cachexia and anorexia. TNF can be lethal.

TNF-α convertase is a metalloproteinase involved in the formation of active TNF-α. Inhibition of TNF-α convertase inhibits production of active TNF-α. Compounds that inhibit both MMPs activity have been disclosed in, for example PCT Publication WO 94/24140. Other compounds that inhibit both MMPs activity have

also been disclosed in WO 94/02466. Still other compounds that inhibit both MMPs activity have been disclosed in WO 97/20824.

There remains a need for effective MMP and TNF-α convertase inhibiting agents. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature* 376, 555-557 (1994)). McGeehan et al., *Nature* 376, 558-561 (1994) also reports such findings.

MMPs are involved in other biochemical processes in mammals as well. Included is the control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β-Amyloid Precursor Protein) to the amyloid plaque and inactivation of α_1-protease inhibitor (α_1-PI). Inhibition of these metalloproteases permits the control of fertility and the treatment or prevention of Alzheimers Disease. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor drug or biochemical such as α_1-PI supports the treatment and prevention of diseases such as emphysema, pulmonary diseases, inflammatory diseases and diseases of aging such as loss of skin or organ stretch and resiliency.

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin (MMP-3), gelatinase (MMP-2), or collagenase III (MMP-13) are the relatively most important enzyme or enzymes to inhibit especially when compared with

collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile.

Inhibitors of metalloproteases are known. Examples include natural biochemicals such as tissue inhibitor of metalloproteinase (TIMP), α_2-macroglobulin and their analogs or derivatives. These are high molecular weight protein molecules that form inactive complexes with metalloproteases. An integer of smaller peptide-like compounds that inhibit metalloproteases have been described. Mercaptoamide peptidyl derivatives have shown ACE inhibition *in vitro* and *in vivo*. Angiotensin converting enzyme (ACE) aids in the production of angiotensin II, a potent pressor substance in mammals and inhibition of this enzyme leads to the lowering of blood pressure.

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO 95/12389. Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are also shown in WO 96/11209. Still furhter Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are shown in U.S. Patent No. 4,595,700. Hydroxamate group-containing MMP inhibitors are disclosed in a number of published patent applications that disclose carbon back-boned compounds, such as in WO 95/29892. Other published patents include WO 97/24117. Additionally, EP 0 780 386 further discloses hydroxamate group-containing MMP inhibitors. WO 90/05719 disclose hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones. WO 93/20047 also discloses hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones. Additionally, WO

95/09841 discloses disclose hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. And WO 96/06074 further discloses hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. Schwartz et al., *Progr. Med. Chem., 29*:271-334(1992) also discloses disclose hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. Furthermore, Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997) discloses hydroxamates that have peptidyl back-bones or peptidomimetic back-bones. Also, Denis et al., *Invest. New Drugs, 15(3)*: 175-185 (1997) discloses hydroxamates that have a peptidyl back-bones or peptidomimetic back-bones as well.

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamate known as batimastat is reported to exhibit IC_{50} values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic hydroxamate was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC_{50} value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997).

Meta analysis of data from Phase I/II studies using marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, prostate), indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological

activity. The most common drug-related toxicity of marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction permits treatment to continue. Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

In view of the importance of hydroxamate MMP inhibitor compounds in the treatment of several diseases and the lack of enzyme specificity exhibited by two of the more potent drugs now in clinical trials, it would be beneficial to use hydroxamates of greater enzyme specificity. This would be particularly the case if the hydroxamate inhibitors exhibited limited inhibition of MMP-1 that is relatively ubiquitous and as yet not associated with any pathological condition, while exhibiting quite high inhibitory activity against one or more of MMP-2, MMP-9 or MMP-13 that are associated with several pathological conditions.

Non-limiting examples of matrix metalloproteinase inhibitors that may be used in the present invention are identified in Table No. 5, below.

Table No. 5. Matrix metalloproteinase inhibitors.

Compound	Trade Name	Reference	Dosage
Biphenyl hydroxamate		WO 97/18188	
	AG-3067 (Agouron	Winter Conf. Med. Bio-	

Compound	Trade Name	Reference	Dosage
	Pharm. Inc.)	organic Chem. 1997 January, 26-31	
	AG-3340 (Agouron Pharm. Inc.)	WO 97/20824	50 mg/kg treatment of Lewis lung carcinomas in test animals
	AG-2024 (Agouron Pharm. Inc.).		
	AG-3365 (Agouron Pharm. Inc.)		
3(S)-N-hydroxy-4-(4-[4-(imidazol-1-yl)phenoxy]benzenesulfonyl)-2,2-dimethyl-tetrahydro-2H-1,4-thiazine-3-carboxamide, and derivatives thereof		WO 97/20824. FEBS (1992) 296 (3):263	In female Lewis rats, arthritis model: dose of 25 mg/kg/day gave 97.5% weight loss inhibition
Heteroaryl		WO 98/17643	

Compound	Trade Name	Reference	Dosage
succinamides derivatives			
	AG-3296 (Agouron Pharm. Inc.)		
	AG-3287(Agouron Pharm. Inc.)		
	AG-3293 (Agouron Pharm. Inc.)		
	AG-3294 (Agouron Pharm. Inc.)		
	AG-3067 (Agouron Pharm. Inc.)	Winter Conf Med Bio-organic Chem 1997 January 26-31	
2R,4S)-4-hydroxy-2-isobutyl-5-mercapto-N-[(1S)-2,2-dimethyl-1-methylcarbamoylpropyl]		EP 0818443	

Compound	Trade Name	Reference	Dosage
pentanamide			
N-alkyl, N-phenylsulfonyl-N`-hydroxamic acid derivatives of heteroaryl carboxylic acids		WO 98/16520	
Novel N-alkyl, N-phenylsulfonyl-N`-hydroxamic acid derivatives of heteroaryl carboxylic acids		WO 98/16514	
Novel N-alkyl, N-phenylsulfonyl-N`-hydroxamic acid derivatives of cycloalkane carboxylic acids		WO 98/16506	
Novel N-alkyl, N-phenylsulfonyl-N`-hydroxamic acid derivatives of anthranilic acid		WO 98/16503	
sulfonamido-hydroxamic acid derivatives		EP 03/98753	

Compound	Trade Name	Reference	Dosage
TIMP-3: polynucleotides encoding endogenous (human) peptides		WO 95/09918	
(3alpha, 5beta,6alpha,7alphabeta)-4`,4`-(hexahydro-2,2-dimethyl-1,3-benzodioxole-5, 6-diyl)bis(2,6-piperazinedione) and derivatives thereof		WO 93/23075	
	BE-16627B	WO 91/08222. Int. J. Cancer 1994 58 5 730 - 735	
(2S)-4-(4-(4-chlorophenyl)phenyl)-4-oxo- 2-(2-phthalimidoethyl)butanoic acid		WO 96/15096	
	Bay-12-9566	WO 96/15096	10 to 400 mg/day
4-oxo-2-(2-phthalimidoethyl) alkanoic acid		WO 97/43238	

Compound	Trade Name	Reference	Dosage
derivatives			
Novel 4-(4-Alkynylphenyl) 4-oxobutanoic acid derivatives		WO 97/43237	
Substituted 4-biarylbutyric or 5-biarylpentanoic acids and derivatives		WO 96/15096	
Substituted 4-biphenyl-4-hydroxybutyric acid derivatives		WO 98/22436	
2R,S)-HONH-CO-CH(i-Bu)-CO-Ala-Gly-NH2,		J Med Chem 1998 41 3 339 -345	
batimastat; BB-94; Hydroxamic acid based collagenase inhibitors		WO 90/05719	15 to 135 mg/m2 administer-ed intra-pleurally
Hydroxamic acid based collagenase inhibitors		WO 90/05719	
marimastat BB-2516; Hydroxamic acid derivatives		WO 94/02447	5 to 800 mg daily
alpha-cycloalkyl		Bio-organic	

Compound	Trade Name	Reference	Dosage
analogs of marimastat		Med Chem Lett 1998 8 11 1359 - 1364	
	GI-245402 (BB-2983)		
Hydroxamic acid derivatives		WO 94/21625	
Succinyl hydroxamic acid, N-formyl-N-hydroxy amino carboxylic acid and succinic acid amide derivatives		WO 95/32944	
hydroxamic acid, N-formyl-N-hydroxyamino and carboxylic acid derivatives,		WO 97/19053	
pseudopeptide hydroxamic and carboxylic acid derivatives from the corresponding lactone and alpha-amino acid		WO 97/19050	
Succinic acid amide		WO 97/03966. GB 95/00111.	

Compound	Trade Name	Reference	Dosage
derivatives		GB 95/00121.	
Hydroxamic acid derivatives		WO 97/02239	
Succinamidyl (alpha substituted) hydroxamic acid derivatives		WO 96/33165	
(2S,3R)-3-[2,2-dimethyl-1S-(thiazol-2-ylcarbamoyl)pro-pylcarbamoyl]-5-methyl-2-(prop-2-enyl)hexano-hydroxanic acid and derivatives thereof		WO 96/25156	
Hydroxamic or carboxylic acid derivatives		WO 96/16931	
hydroxamic and carboxylic acids		WO 96/06074	
2-[(1S)-1-((1R)-2-[[1,1`-biphenyl]-4-ylmethylthio]-1-[(1S)-2,2-dimethyl-1-(methylcarbamoyl)propylcarbamoyl		WO 98/23588	

Compound	Trade Name	Reference	Dosage
]ethylcarbamoyl) -4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butylthio]-acetate, and derivatives thereof			
Hydroxamic acid derivatives as inhibitors of cytokine production		WO 95/09841	
Hydroxamic acid derivatives		WO 94/24140	
Aromatic or heteroaryl substituted hydroxamic or carboxylic acid derivatives		WO 95/19956	
Hydroxamic acid derivatives		WO 95/19957	Doses are preferably 1 to 100 mg/kg.
Hydroxamic acid and carboxylic acid derivatives		WO 95/19961	Doses are preferably 1 to 100 mg/kg.
Butanediamide, N1-	BB-1433		At 50 mg/kg bid. p.o.

Compound	Trade Name	Reference	Dosage
[1(cyclohexyl-methyl)-2 (methylamino)-2-oxoethyl]-N4,3-dihydroxy-2-(2-methylpropyl)-, [2R[N1(S*),2R*,3 S*]]-			inhibited bone mineral density loss
tetracycline analogs and D-penicillamine		EP 733369	D-penicill-amine reduced allergic encephaliti s symptom scores in a dose dependent manner at 27, 125 and 375 mug with complete inhibition
	CDP-845	Biochem Pharmacol 1990 39 12 2041-2049	
succinamide derivatives		WO 95/04033	oral bioavail-ability by murine

Compound	Trade Name	Reference	Dosage
			pleural cavity assay in the presence of gelatinase: Between 73% and 100% inhibition was displayed at 10 mg/kg for six of the compounds. The seventh displayed 100% inhibition at 80 mg/kg.
Peptidyl derivatives		WO 94/25435. WO 94/25434	
Mercaptoalkyl-peptidyl compounds having an imidazole substituent		WO 97/19075	
mercaptoalkyl-peptide derivatives		WO 97/38007. WO 95/12389. WO 96/11209.	

Compound	Trade Name	Reference	Dosage
Mercaptoalkyl-amide derivatives		WO 97/37974	
arylsulfonyl-hydrazine derivatives		WO 97/37973. WO 95/12389	
N-acetylthio-lacetyl-N-(3-phthalimidopropy l)-L-leucyl-L-phenylalanine N-methylamide		WO 96/35714	
2-acetylsulfany-l-5-phthalimido-pentanoyl-L-leucineN-(2-phenylethyl)-amide		WO 96/35712	dosages of about 0.5 mg to 3.5 g per day for the treatment of inflam-mation
5-phthalimido-pentanoyl-L-leucyl-L-phenylalanineN-methylamide		WO 96/35711	
peptidyl derivatives		WO 98/06696	
4-[4-(methoxycarbonyl methoxy)-3,5-dimethylphenyl]-		WO 98/05635	

Compound	Trade Name	Reference	Dosage
2-methyl-1(2H)-phthalazinone, and hydroxamic and carboxylic acid derivatives			
thio-substituted peptides		WO 97/12902	
Mercaptoamides		WO 97/12861	
Peptidyl derivatives having SH or acylo groups which are amides, primary amides or thioamides		WO 96/35687	
	D-5410 (Chiro-science Group plc)		
		WO 95/13289	
	CH-104, (Chiro-science Group plc)		
	D-2163 (Chiro Science Ltd.)		
	D-1927 (Chiro		

Compound	Trade Name	Reference	Dosage
	Science Ltd.)		
	Dermastat (Colla-Genex Phar-maceu-tical Inc.)		
	Metastat (Colla-Genex)		
	Osteostat (Colla-Genex Phar-maceu-tical Inc.)		
	doxy-cycline; Roche; Periostat		Gingival crevicular fluid collagenase is reported to be inhibited at concentra-tions of 5-10 microg /ml or 15-

Compound	Trade Name	Reference	Dosage
			30 microM
2S, 5R, 6S-3-aza-4-oxo-10-oxa-5-isobutyl-2-(N-methylcarbox-amido)-[10]paracyclophane-6-N-hydroxycarboxamide		WO 97/18207	
hydroxamic acid and amino-carboxylate compounds		WO 96/33176	
N-hydroxamic derivatives of succinamide		WO 96/33166	
Macrocyclic amino carboxylates		J Med Chem 1998 41 11 1749-1751	
	SE-205 (Du Pont Merck Pharm Co.)	Bio-organic Med Chem Lett 1998 8 7 837-842. J Med Chem 1998 41 11 1745 -1748	
macrocyclic matrix metalloprotease-			

Compound	Trade Name	Reference	Dosage
8 inhibitors			
Hydroxamic acid and carboxylic acid derivatives		WO 95/22966	
succinamid derivatives		US 5256657	
mercaptosulfide derivatives		WO 95/09833	
sulfoximine and sulfodiimine derivatised peptides		WO 95/09620	
water soluble MMP inhibitors		WO 96/33968	
hydantoin derivatives		EP 06/40594	
Piperazine derivatives		WO 98/27069	
	GI-155704A	J Med Chem 1994 37 5 674. Bioorganic Med Chem Lett 1996 6 16 1905 - 1910	
Cyclic imide derivatives.		EP 05/20573	
3-(mercapto-methyl) hexa-		WO 97/48685	

Compound	Trade Name	Reference	Dosage
hydro-2,5-pyrazinedione derivatives			
beta-mercaptoketone and beta-mercaptoalcohol derivatives		WO 96/40738	
	ilomastat MPI; GM-6001; Galardin	US 5114953. Cancer Res 1994 54 17 4715-4718	eye drops containing ilomastat (800 microg/ml)
Cyclic and heterocyclic N-substituted alpha-iminohydroxamic and carboxylic acids		WO 97/18194	
Aminomethyl-phosphonic and aminomethyl-phosphinic acids derivatives		EP 703239	
3-Mercapto-acetylamino-1,5-substituted-2-oxo-azepan derivatives		WO 98/12211	
2-substituted		WO 94/04531	

Compound	Trade Name	Reference	Dosage
indane-2-mercaptoacetyl-amide tricyclic derivatives			
	Ro-2756 (Roche Holding AG)		
	Ro-26-4325 (Roche Holding AG)		
	Ro-26-5726 (Roche Holding AG)		
	Ro-26-6307 (Roche Holding AG)		
	Ro-31-9790 (Roche Holding AG)	J Am Soc Nephrol 1995 6 3 904. Inflamm Res 1995 44 8 345 -349	mono-arthritis in rat: 100 mg/kg/day
substituted and unsubstituted hydroxamates (specifically N-[D,L-2-isobutyl-		WO 92/09556	

Compound	Trade Name	Reference	Dosage
3-(N'-hydroxy-carbonyl-amido)-propanoyl]trypto phanmethylamide)			
GM6001, N-(2(R)-2 -(hydroxyaminocar bonylmethyl)-4-methylpentanoyl)-L-tryptophan methylamide.		WO 95/24921	
Oligonucleotice (c-jun)			
Sulfated polysaccharides		WO 98/11141	
	KB-R7785; KB-R8301; KB-R8845	Life Sci 1997 61 8 795-803	
Fas ligand solubilization inhibitor		WO 97/09066	
gelastatin AB, KRIBB			
	KT5-12 (Kotobuki Seiyaku Co Ltd.)	Faseb J 1998 12 5 A773 (4482)	
2-(N2-[(2R)-2-(2-hydroxyamino-2-oxoethyl)-5-(4-		GB 23/18789	

Compound	Trade Name	Reference	Dosage
methoxyphenoxy)pentanoyl]-L-phenylalanylamino)ethanesulfonamide, and carboxylic acid derivatives thereof			
Chromone derivatives		EP 758649	2-Pyrolylthio-chromone in a murine melanoma model produced 37% inhibition at 100 mg/kg
Esculetin derivatives,		EP 719770	
substituted and unsubstituted hyroxyureas and reverse hydroxamates		WO 92/09563	
Synthetic MMP inhibitors (ex. N-(D,L-2-isobutyl-3-(N'-hydroxycarbonyla		WO 94/22309	

Compound	Trade Name	Reference	Dosage
mido)propanoyl)t ryptophan methylamide)			
Reverse hydroxamates and hydroxyureas		WO 95/19965	in female mice infected w/murine melanoma - init 80 mu g followed by 150 mg/kg/day
N-(mercaptoacyl)-aryl derivatives of leucine and phenylalanine		US 5629343	
N-carboxyalkyl derivatives		WO 95/29689	
Substituted cyclic derivatives		GB 22/82598	Inflammation is stated to be effectively treated by oral administration of 0.01 to 50 mg/kg
Substituted n-carboxyalkyldi-peptides		GB 22/72441	

Compound	Trade Name	Reference	Dosage
(2S,4R)-2-methyl-4-(phenylamino-carbonylmethyl-aminocarbonyl)-6-(4-propyl-phenyl)hexanoic acid, and carboxylic acid derivatives		WO 97/11936	
Substituted cyclic derivatives		US 5403952	
Thiol sulfonamide metalloprotease inhibitors		WO 98/03166	
Thiol sulfone metalloprotein-ase inhibitors		WO 98/03164	
formulations containing vanadium compounds and N-acetylcysteine		WO 97/47296	
	NSC-683551; COL-3 (National Cancer Institute)		

Compound	Trade Name	Reference	Dosage
	BB-3644 (Neures Ltd.)		
Arylsulfonamido-substituted hydroxamic acids	CGS-27023A; CGS-25966	Int Congr Inflamm Res Assoc 1994 7th Abs 73. EP-00606046	600 mg tid (Ph I - colorectal and melanoma patients); 100 mg/kg in food in osteoarthritis model rabbits
alpha-Substituted arylsulfonamido hydroxamic acid derivatives		WO 97/22587	
Arylsulfonamido-substituted hydroxamic acids		US 5455258	active at 30 mg/kg in in vivo assay
Arylsulfonamido-substituted hydroxamic acids		WO 96/00214	
2S,3S)-N-hydroxy-5-methyl-2-[2-(2-methoxyethoxy)ethoxymethyl]-3-		WO 98/14424	

Compound	Trade Name	Reference	Dosage
(N-[(1S)-1-(N-methylcarbamoyl)-2-phenylethyl]carbamoyl)hexanamide and Hydroxamic acid derivatives			
arylsulfonamido-substituted hydroxamic acids		WO 96/40101	in tumor model mice: administered for 7 to 17 days at a dosage of 30 mg/kg twice daily
Aryl (sulfide, sulfoxide and sulfone) derivatives		WO 97/49679	
Phenylsulfonamide derivatives		WO 97/45402	
Arylsulfonamido-aminoacid derivative		EP 757037	
A1PDX (Oregon Health Sciences University)			
futoenone analogs		Bio-organic Med Chem	

Compound	Trade Name	Reference	Dosage
		Lett 1995 5 15 1637 - 1642	
debromohymeni-aldisine and related compounds		WO 96/40147	preferred 1-30 mg/day
amide derivatives of 5-amino-1,3,4-thiadiazolones		WO 96/40745	
3S-(4-(N-hydroxylamino)-2R-isobutylsuccinyl)amino-1-methoxymethyl-3,4-dihydrocarbostyril and deriviatives therof		WO 94/21612	
Carbostyryl derivatives		JP 8325232	
OPB-3206 (Otsuka Pharmaceutical Co, Ltd.)			
Arylsulfonyl hydroxamic acid derivatives		WO 96/33172	
Cyclic sulfone		EP 818442	

Compound	Trade Name	Reference	Dosage
derivatives			
arylsulfonamido N-hydroxamic acid derivatives of butyric acid		WO 96/27583	
Arylsulfonyl-amino hydroxamic acid derivatives		WO 98/07697	
phosphinate-based derivatives		WO 98/03516	
cyclopentyl-substituted glutaramide derivatives		WO 92/14706	
N-hydroxamic acid succinamide derivatives		WO 97/49674	
Thiadiazole amide MMP inhibitors.		WO 97/48688	
(S)-1-[2-[[[(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)amino]-carbonyl]amino]-1-oxo-3-(pentafluoro-phenyl)propyl]-4-(2-pyridinyl)-		WO 97/40031	

Compound	Trade Name	Reference	Dosage
piperazine			
hydroxamic acid derivatives of pyrrolidone-3-acetamide.		WO 97/32846	
alpha-arylsulfonamido-N-hydroxamic acid derivatives		WO 98/17645	
beta-Sulfonylhydroxamic acids		WO 98/13340	
Hydroxamic acid derivatives		US 5712300	
	PNU-99533 (Pharmacia & UpJohn Inc.)		
	PNU-143677 (Pharmacia & UpJohn Inc.)		
	POL-641 (Poli-farma)		
Peptidomimetic inhibitors		WO 96/20,18. WO 96/29313. WO 98/08814. WO 98/08815. WO 98/08850. WO 98/08822.	

Compound	Trade Name	Reference	Dosage
		WO 98/08823. WO 98/08825. WO 98/08827.	
2R)-N-hydroxycarboxami demethyldecanoic acid amide of 1N-(carbomethoxy-methyl)	()-caprol-actam-(3S)-amine	WO 96/29313	rheumatoid arthritis: female subject - 50 mg po for 2 yrs; male subject - 70 mg po daily for 5 yrs; corneal ulcer: male subject 0 10 mg in saline soln for 2 months, 2 times/day
3-(N-[(N-Hydroxyaminocarb onyl)methyl]-N-isobutylaminocar bonyl)-2-(R)-isobutylpro-panoyl-L-phenylalanine		WO 96/20918	

Compound	Trade Name	Reference	Dosage
amide			
N-hydroxy-phosphinic acid amides		WO 98/08853	
N`-arylsulfonyl derivatives of spirocyclic-N-hydroxycarbox-amides		WO 98/08850	
N`-arylsulfonyl derivatives of thiazepinone and azepinone-N-hydroxycarbox-amides		WO 98/08827	
Substituted piperazine derivatives		WO 98/08825	
N`-arylsulfonyl derivatives of pyrimidine, thiazepine and diazepine-N-hydroxycarbox-amides		WO 98/08823	
Substituted pyrrolidine derivatives		WO 98/08815	
Substituted heterocycles		WO 98/08814	
Substituted 1,3-		WO 09/08822	

Compound	Trade Name	Reference	Dosage
diheterocyclic derivatives			
substituted 5-amino-1,2,4-thiadiazole-2-thiones		WO 98/25949	
Hydroxamic acid derivatives which inhibit TNF production.		WO 97/24117	
6-methoxy-1,2,3,4-tetrahydro-norharman-1-carboxylic acid		WO 97/37658	
	RS-130830	Arthritis Rheum 1997 40 9 SUPPL. S128	
Aralkyl MMP inhibitors (ex. N-(2R-carboxymethyl-5-(biphen-4-yl)pentanoyl)-L-t-butylglycine-N'-(pyridin-4-yl)carboxamide)		WO 96/16027	
	Ro-32-3555 (Roche Holding		

Compound	Trade Name	Reference	Dosage
	AG)		
	Ro-32-1278 (Roche Holding AG)		
	Ro-32-1541 (Roche Holding AG)		
	Ro-31-3790 (Roche Holding AG)		Arthritic model rats: Protection of cartilage degradation following oral administration; ED50 = 10 mg/kg po
(3R,11S)-N-hydroxy-5-methyl-3-(10-oxo-1,9-diazatricyclo-(11.6.1.014,19)eicosa-13(20),14(19),15,17-tetraen- 11-ylcarbamoyl)hexanamide and		WO 95/04735	

Compound	Trade Name	Reference	Dosage
derivatives thereof			
Bridged indoles (Roche Holding AG)		WO 96/23791	
substituted phenylsulfonyl acetamide, propionamide and carboxamide compounds		EP 780386	
5-(4'-biphenyl)-5-[N-(4-nitrophenyl) piperazinyl] barbituric acid		WO 97/23465	
Malonic acid based matrix metalloproteinase inhibitors		EP 716086	
phenyl carboxamide derivatives		WO 95/12603	
Malonic acid based mmp inhibitors (specifically 2-(4-acetylamino-benzoyl)-4-methylpentanoic acid)		EP 716086	

Compound	Trade Name	Reference	Dosage
Hydroxyl amine derivatives	Ro-31-4724; Ro-31-7467;	EP 236872	

The following individual patent references listed in Table No. 6 below, hereby individually incorporated by reference, describe various MMP inhibitors suitable for use in the present invention described herein, and processes for their manufacture.

Table No. 6. MMP inhibitors

EP 189784	US 4609667	WO 98/25949	WO 98/25580
JP 10130257	WO 98/17655	WO 98/17645	US 5760027
US 5756545	WO 98/22436	WO 98/16514	WO 98/16506
WO 98/13340	WO 98/16520	WO 98/16503	WO 98/12211
WO 98/11908	WO 98/15525	WO 98/14424	WO 98/09958
WO 98/09957	GB 23/18789	WO 98/09940	WO 98/09934
JP 10045699	WO 98/08853	WO 98/06711	WO 98/05635
WO 98/07742	WO 98/07697	WO 98/03516	WO 98/03166
WO 98/03164	GB 23/17182	WO 98/05353	WO 98/04572
WO 98/04287	WO 98/02578	WO 97/48688	WO 97/48685
WO 97/49679	WO 97/47599	WO 97/43247	WO 97/43240
WO 97/43238	EP 818443	EP 818442	WO 97/45402
WO 97/40031	WO 97/44315	WO 97/38705	US 5679700
WO 97/43245	WO 97/43239	WO 97/43237	JP 09227539
WO 97/42168	US 5686419	WO 97/37974	WO 97/36580
WO 97/25981	WO 97/24117	US 5646316	WO 97/23459
WO 97/22587	EP 780386	DE 19548624	WO 97/19068

WO 97/19075	WO 97/19050	WO 97/18188	WO 97/18194
WO 97/18183	WO 97/17088	DE 19542189	WO 97/15553
WO 97/12902	WO 97/12861	WO 97/11936	WO 97/11693
WO 97/09066	JP 09025293	EP 75/8649	WO 97/03966
WO 97/03783	EP 75/7984	WO 97/02239	WO 96/40745
WO 96/40738	WO 96/40737	JP 08/311096	WO 96/40204
WO 96/40147	WO 96/38434	WO 96/35714	WO 96/35712
WO 96/35711	WO 96/35687	EP 74,3,070	WO 96/33968
WO 96/33165	WO 96/33176	WO 96/33172	WO 96/33166
WO 96/33161	GB 23/00190	WO 96/29313	EP 73/6302
WO 96/29307	EP 733369	WO 96/26223	WO 96/27583
WO 96/25156	GB 22/98423	WO 96/23791	WO 96/23505
GB 22/97324	DE 19501032	WO 96/20918	US 5532265
EP 719770	WO 96/17838	WO 96/16931	WO 96/16648
WO 96/16027	EP 716086	WO 96/15096	JP 08104628
WO 96/13523	JP 08081443	WO 96/11209	EP 703239
WO 96/06074	WO 95/35276	WO 96/00214	WO 95/33731
WO 95/33709	WO 95/32944	WO 95/29892	WO 95/29689
CA 21/16924	WO 95/24921	WO 95/24199	WO 95/23790
WO 95/22966	GB 22/87023	WO 95/19965	WO 95/19961
WO 95/19956	WO 95/19957	WO 95/13,289	WO 95/13380
WO 95/12603	WO 95/09918	WO 95/09841	WO 95/09833
WO 95/09620	WO 95/08327	GB 22/82598	WO 95/07695
WO 95/05478	WO 95/04735	WO 95/04033	WO 95/02603
WO 95/02045	EP 626378	WO 94/25435	WO 94/25434
WO 94/21612	WO 94/24140	WO 94/24140	EP 622079
WO 94/22309	JP 06256209	WO 94/21625	FR 27/03053
EP 606046	WO 94/12169	WO 94/11395	GB 22/72441
WO 94/07481	WO 94/04190	WO 94/00119	GB 22/68934
WO 94/02446	EP 575844	WO 93/24475	WO 93/24449
US 5270326	US 5256657	WO 93/20047	WO 93/18794

WO 93/14199	WO 93/14096	WO 93/13741	WO 93/09090
EP 53/2465	EP 532156	WO 93/00427	WO 92/21360
WO 92/09563	WO 92/09556	EP 48/9579	EP 489577
US 5114953	EP 45/5818	US 5010062	AU 90/53158
WO 97/19075	US 7488460	US 7494796	US 7317407
EP 277428	EP 23/2027	WO 96/15096	WO 97/20824
US 5837696			

The Marimastat used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 94/02,447.

The Bay-12-9566 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 96/15,096.

The AG-3340 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/20,824.

The Metastat used in the therapeutic combinations of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,837,696.

The D-2163 used in the therapeutic combinations of the present invention can be prepared in the manner set forth in WO 97/19,075.

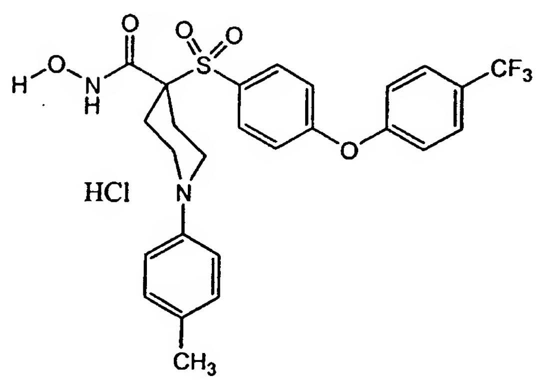
More preferred zinc matrix metalloproteinase inhibitors include those described in the individual U.S. Patent applications, PCT publications and U.S. Patents listed below in Table No. 7, and are hereby individually incorporated by reference.

Table No. 7. More preferred zinc matrix metalloproteinase inhibitors

U.S. Patent Application Serial Number 97/12,873
U.S. Patent Application Serial Number 97/12,874
U.S. Patent Application Serial Number 98/04,299
U.S. Patent Application Serial Number 98/04,273
U.S. Patent Application Serial Number 98/04,297
U.S. Patent Application Serial Number 98/04,300
U.S. Patent Application Serial Number 60/119,181
WO 94/02447
WO 96/15096
WO 97/20824
WO 97/19075
US 5837696

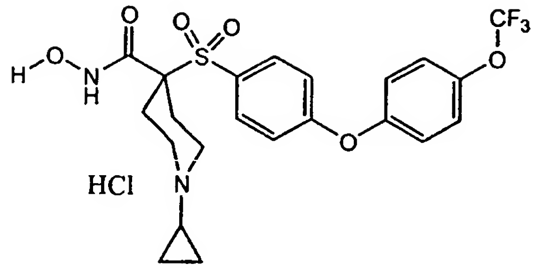
Even more preferred zinc matrix metalloproteinase inhibitors that may be used in the present invention include:

M1)



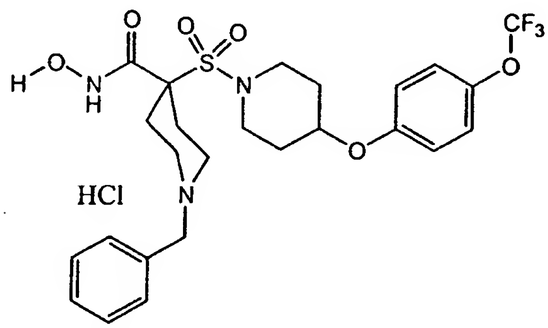
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M2)



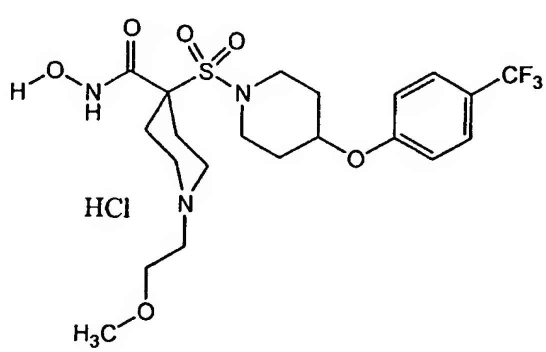
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M3)



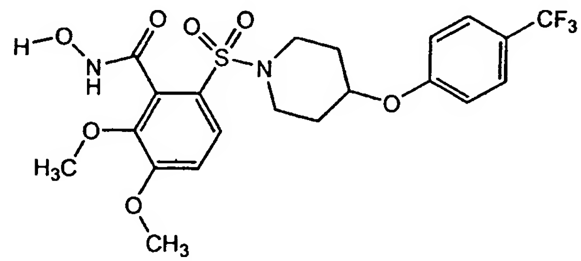
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M4)



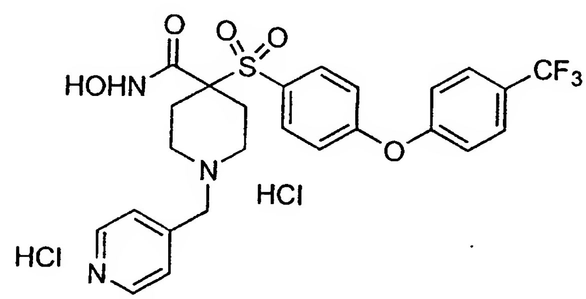
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M5)



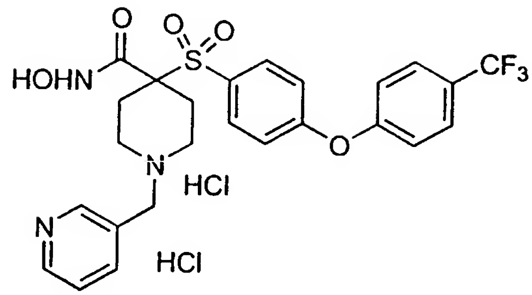
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide;

M6)



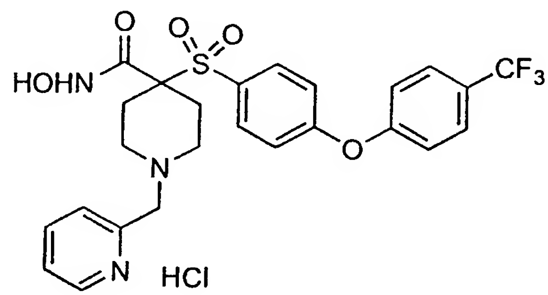
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M7)



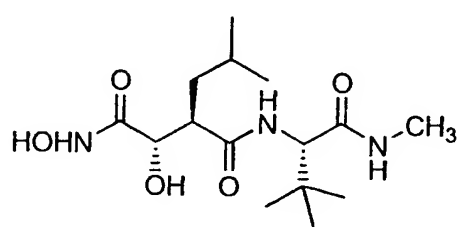
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M8)



N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

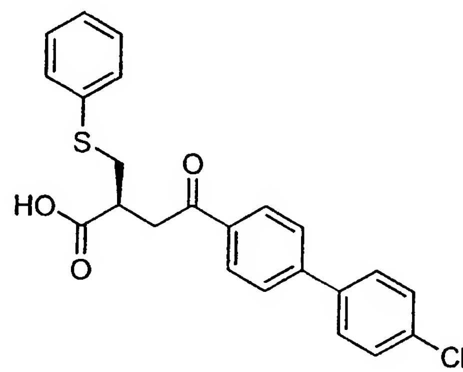
9)



British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-

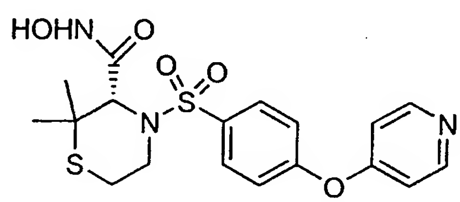
N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-);

M10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid;

M11)

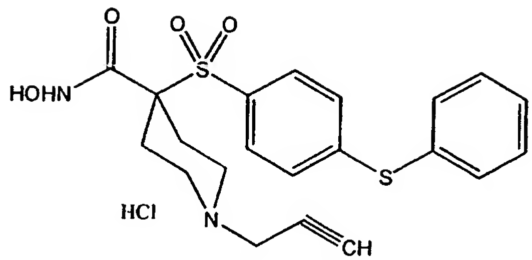


Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2 dimethyl- 4-[[4-(4-pyridinyloxy)phenyl]-sulfonyl]- 3-thiomorpholinecarboxamide;

M12) CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline;

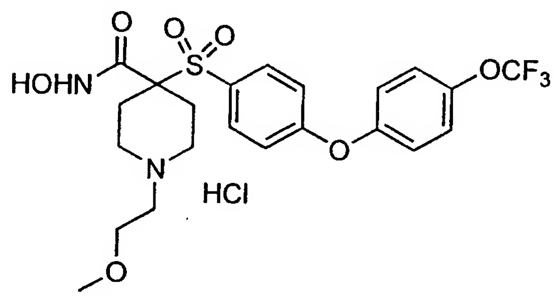
M13) Chiroscience D-2163, 2-[1S- ([(2R,S)-acetylmercapto-5-phthalimido]pentanoyl-L-leucyl)amino-3-methylbutyl]imidazole;

M14)



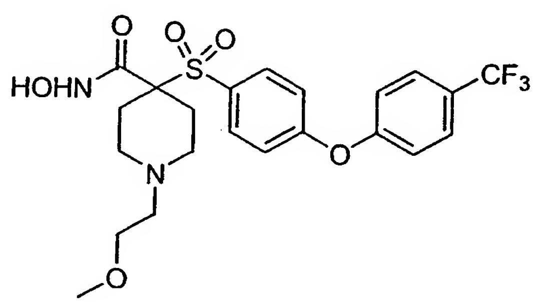
N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride;

M15)



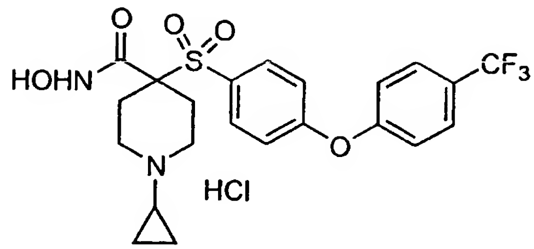
N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M16)



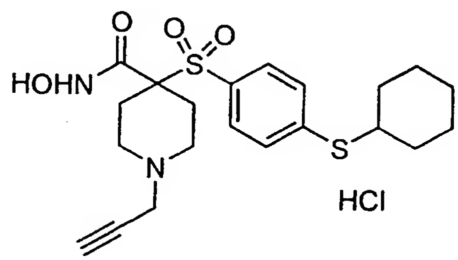
N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinearboxamide;

M17)



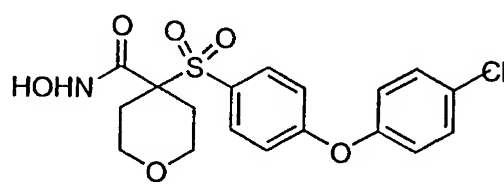
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M18)



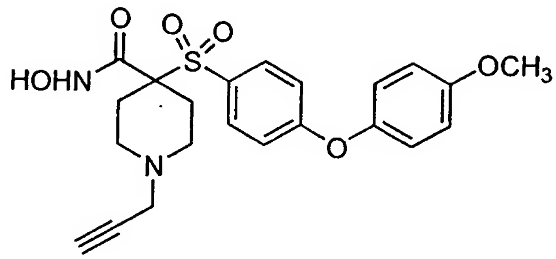
4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride;

M19)



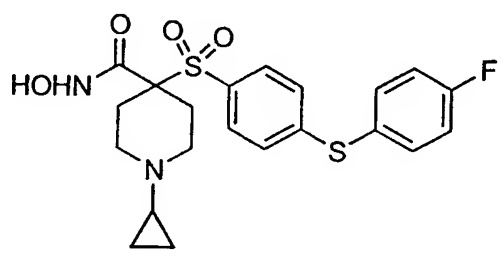
4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

M20)



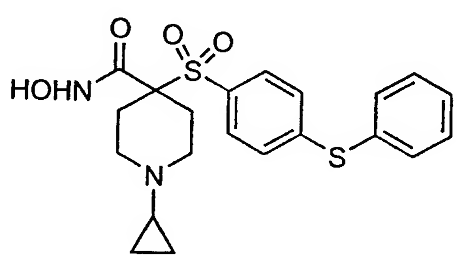
N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide;

M21)



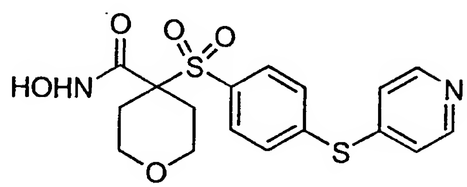
1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide;

M22)



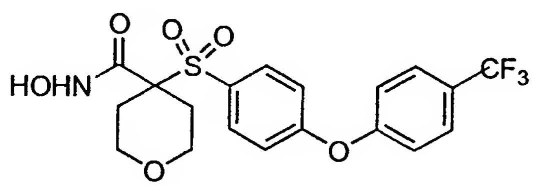
1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide;

M23)



tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide;

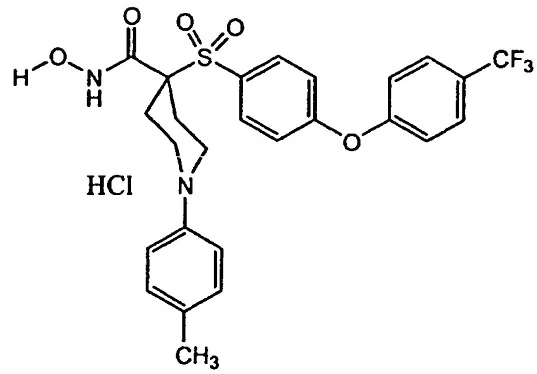
M24)



tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide.

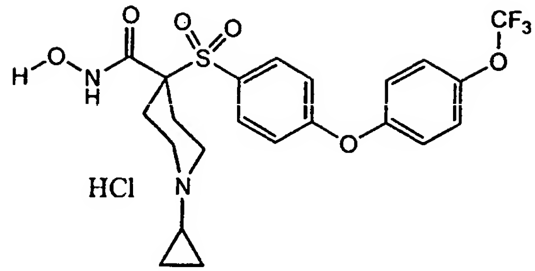
Still more preferred MMP inhibitors include:

M1)



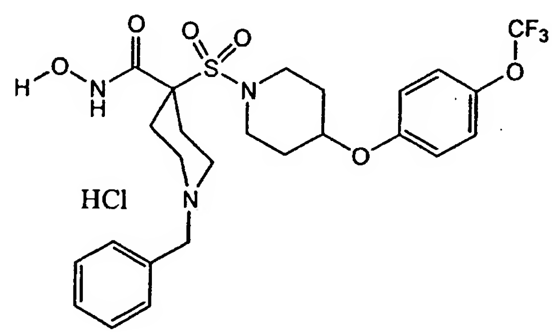
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M2)



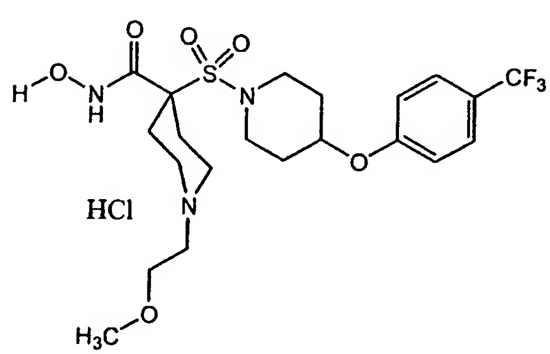
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M3)



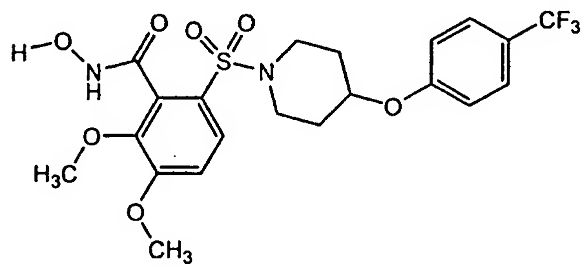
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M4)



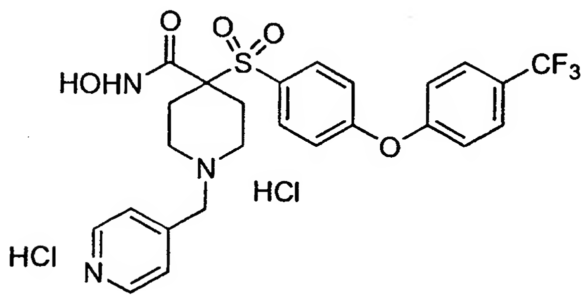
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M5)



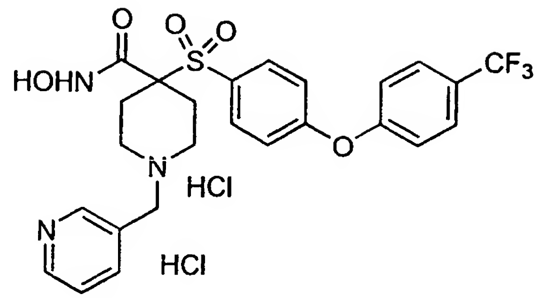
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide;

M6)



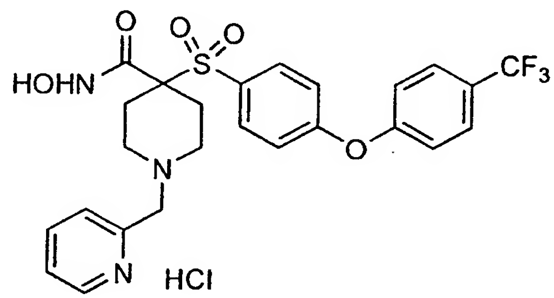
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M7)



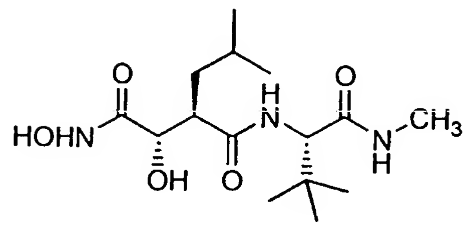
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

M8)



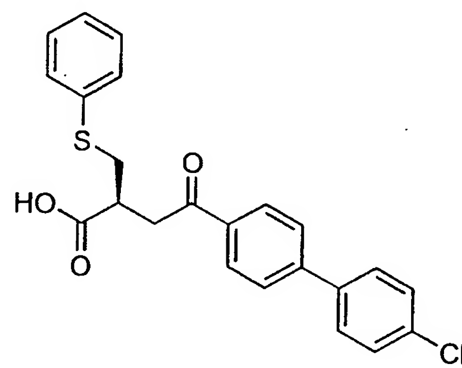
N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

M9)



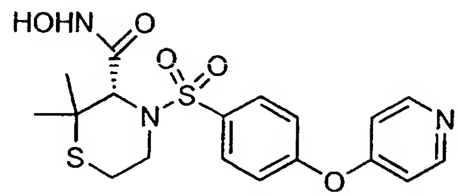
British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-N1,2 -dihydroxy-3 (2- methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-);

M10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid;

M11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2- dimethyl- 4-[[4-(4-pyridinyloxy)phenyl] sulfonyl]- 3- thiomorpholinecarboxamide;

M12) CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline;

M13) Chiroscience D-2163, 2- [1S- ([(2R,S)-acetylmercapto- 5- phthalimido]pentanoyl- L-leucyl)amino- 3- methylbutyl]imidazole.

Dosage of MMP Inhibitors

Dosage levels of MMP inhibitors on the order of about 0.1 mg to about 10,000 mg of the active ingredient compound are useful in the treatment of the above conditions, with preferred levels of about 1.0 mg to about 1,000 mg. The amount of active ingredient that may be combined with other anticancer agents to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate

of excretion, drug combination, and the severity of the particular disease being treated and form of administration.

Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present invention. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Generally speaking, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro. Thus, where an compound is found to demonstrate in vitro activity at, e.g., 10 μM, one will desire to administer an amount of the drug that is effective to provide about a 10 μM concentration in vivo. Determination of these parameters are well within the skill of the art.

These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

<u>Administration Regimen</u>

Any effective treatment regimen can be utilized and readily determined and repeated as necessary to effect treatment. In clinical practice, the compositions

containing a MMP inhibitor alone or in combination with other therapeutic agents are administered in specific cycles until a response is obtained.

For patients who initially present without advanced or metastatic cancer, a MMP inhibitor in combination with radiation therapy, is used as a continuous post-treatment therapy in patients at risk for recurrence or metastasis (for example, in adenocarcinoma of the prostate, risk for metastasis is based upon high PSA, high Gleason's score, locally extensive disease, and/or pathological evidence of tumor invasion in the surgical specimen). The goal in these patients is to inhibit the growth of potentially metastatic cells from the primary tumor during surgery and inhibit the growth of tumor cells from undetectable residual primary tumor.

For patients who initially present with advanced or metastatic cancer, a MMP inhibitor in combination with radiation therapy of the present invention is used as a continuous supplement to, or possible replacement for hormonal ablation. The goal in these patients is to slow or prevent tumor cell growth from both the untreated primary tumor and from the existing metastatic lesions.

Illustrations

The following discussion highlights some agents in this respect, which are illustrative, not limitative. A wide variety of other effective agents also may be used.

Colorectal Cancer

The preferred combination therapy for the treatment of colorectal cancer is surgery, followed by a regimen of one or more chemotherapeutic agents, cycled over a

over a one year time period. In the treatment of colorectal cancer, radiation alone or in combination with surgery and/or chemotherapeutic agents is often used. Preferred chemotherapeutic agents include fluorouracil, and Levamisole. Preferably, fluorouracil and Levamisole are used in combination.

Prostate Cancer

Current therapies for prostate cancer focus upon reducing levels of dihydrotestosterone to decrease or prevent growth of prostate cancer. Radiation alone or in combination with surgery and/or chemotherapeutic agents is often used.

Pancreas Cancer

Preferred combinations of therapy for the treatment of non-metastatic adenocarcinoma include the use of preoperative bilary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant radiation; and chemotherapy. For the treatment of metastatic adenocarcinoma, the preferred chemotherapy consists of 5-fluorouracil, followed weekly cisplatin therapy.

Lung Cancer

In many countries including Japan, Europe and America, the number of patients with lung cancer is fairly large and continues to increase year after year and is the most frequent cause of cancer death in both men and women. Although there are many potential causes

for lung cancer, tobacco use, and particularly cigarette smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in smokers, or radon are contributory factors. Also occupational hazards such as exposure to uranium have been identified as an important factor. Finally, genetic factors have also been identified as another factor that increase the risk of cancer.

Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma(epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell lung cancer (oat cell). Non-small cell lung cancer (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell lung cancer (SCLC). Thus, chemotherapeutic formulas and radiation therapy are different between these two types of lung cancer.

Non-Small Cell Lung Cancer

Where the location of the non-small cell lung cancer tumor can be easily excised (stage I and II disease) surgery is the first line of therapy and offers a relatively good chance for a cure. However, in more advanced disease (stage IIIa and greater), where the tumor has extended to tissue beyond the bronchopulmonary lymph nodes, surgery may not lead to complete excision of the tumor. In such cases, the patient's chance for a cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC tumor, other types of therapies must be utilized.

Today radiation therapy is the standard treatment to control unresectable or inoperable NSCLC. Improved results have been seen when radiation therapy has been

combined with chemotherapy, but gains have been modest and the search continues for improved methods of combining modalities.

Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration but the two most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. A preferred course of treatment for a patient undergoing radiation therapy for NSCLC will be a treatment schedule over a 5 to 6 week period, with a total dose of 50 to 60 Gy administered to the patient in a single daily fraction of 1.8 to 2.0 Gy, 5 days a week. A Gy is an abbreviation for Gray and refers to 100 rad of dose.

However, as NSCLC is a systemic disease, and radiation therapy is a local modality, radiation therapy as a single line of therapy is unlikely to provide a cure for NSCLC, at least for those tumors that have metastasized distantly outside the zone of treatment. Thus, the use of radiation therapy with other modality regimens have important beneficial effects for the treatment of NSCLC.

Generally, radiation therapy has been combined temporally with chemotherapy to improve the outcome of treatment. There are various terms to describe the temporal relationship of administering radiation therapy

and chemotherapy, and the following examples are the preferred treatment regimens and are generally known by those skilled in the art and are provided for illustration only and are not intended to limit the use of other combinations. "Sequential" radiation therapy and chemotherapy refers to the administration of chemotherapy and radiation therapy separately in time in order to allow the separate administration of either chemotherapy or radiation therapy. "Concomitant" radiation therapy and chemotherapy refers to the administration of chemotherapy and radiation therapy on the same day. Finally, "alternating" radiation therapy and chemotherapy refers to the administration of radiation therapy on the days in which chemotherapy would not have been administered if it was given alone.

It is reported that advanced non-small cell lung cancers do not respond favorably to single-agent chemotherapy and useful therapies for advanced inoperable cancers have been limited. (J. Clin. Oncol. 1992, 10, 829-838).

Japanese Patent Kokai 5-163293 refers to 16-membered-ring macrolide antibiotics as a drug delivery carrier capable of transporting anthoracycline-type anticancer drugs into the lungs for the treatment of lung cancers. However, the macrolide antibiotics specified herein are disclosed to be only a drug carrier, and there is no reference to the therapeutic use of macrolides against non-small cell lung cancers.

WO 93/18652 refers to the effectiveness of the specified 16-membered-ring macrolides such as bafilomycin, etc. in treating non-small cell lung cancers, but they have not yet been clinically practicable. Pharmacology, vol. 41, pp. 177-183 (1990)

describes that a long-term use of erythromycin increases productions of interleukins 1, 2 and 4, all of which contribute to host immune responses, but there is no reference to the effect of this drug on non-small cell lung cancers. Tetragenesis, Carcinogenesis, and Mutagenesis, vol. 10, pp. 477-501 (1990) describes that some of antimicrobial drugs can be used as an anticancer agent, but does not refer to their application to non-small cell lung cancers. In addition, interleukins are known to have an antitumor effect, but have not been reported to be effective against non-small cell lung cancers. Any 14 - or 15-membered-ring macrolides have not been reported to be effective against non-small cell lung cancers.

However, several chemotherapeutic agents have been shown to be efficacious against NSCLC. Preferred chemotherapeutic agents against NSCLC include etoposide, carboplatin, methotrexate, 5-fluorouracil, epirubicin, doxorubicin, and cyclophosphamide. The most preferred chemotherapeutic agents active against NSCLC include cisplatin, ifosfamide, mitomycin C, epirubicin, vinblastine, and vindesine.

Other agents that are under investigation for use against NSCLC include: camptothecins, a topoisomerase 1 inhibitor; navelbine (vinorelbine), a microtubule assembly inhibitor; taxol, inhibitor of normal mitotic activity; gemcitabine, a deoxycytidine analogue; fotemustine, a nitrosourea compound; and edatrexate, a antifol.

The overall and complete response rates for NSCLC has been shown to increase with use of combination chemotherapy as compared to single-agent treatment. Haskel, Chest. 1991, 99: 1325; Bakowsk, *Cancer Treat.*

Rev. 1983; 10:159; Joss, *Cancer Treat. Rev.* 1984, 11: 205.

Small Cell Lung Cancer

Approximately 15 to 20 percent of all cases of lung cancer reported worldwide is small cell lung cancer (SCLC). (Ihde, *Cancer* 1984, 54, 2722). Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy, radiation therapy and surgery. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary tumor and persistence of the tumor in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

The most preferred chemotherapeutic agents against SCLC include vincristine, cisplatin, carboplatin, cyclophosphamide, epirubicin (high dose), etoposide (VP-16) I.V., etoposide (VP-16) oral, isofamide, teniposide (VM-26), and doxorubicin. Preferred single-agents chemotherapeutic agents include BCNU (carmustine), vindesine, hexamethylmelamine (altretamine), methotrexate, nitrogen mustard, and CCNU (lomustine). Other chemotherapeutic agents under investigation that have shown activity againe SCLC include iroplatin, gemcitabine, lonidamine, and taxol. Single-agent chemotherapeutic agents that have not shown activity against SCLC include mitoguazone, mitomycin C, aclarubicin, diaziquone, bisantrene, cytarabine, idarubicin, mitomxantrone, vinblastine, PCNU and esorubicin.

The poor results reported from single-agent chemotherapy has led to use of combination chemotherapy.

Additionally, radiation therapy in conjunction MMP inhibitors and systemic chemotherapy is contemplated to

be effective at increasing the response rate for SCLC patients. The typical dosage regimen for radiation therapy ranges from 40 to 55 Gy, in 15 to 30 fractions, 3 to 7 times week. The tissue volume to be irradiated is determined by several factors and generally the hilum and subcarnial nodes, and bialteral mdiastinal nodes up to the thoracic inlet are treated, as well as the primary tumor up to 1.5 to 2.0 cm of the margins.

Breast Cancer

Today, among women in the United States, breast cancer remains the most frequent diagnoses cancer. One in 8 women in the United States at risk of developing breast cancer in their lifetime. Age, family history, diet, and genetic factors have been identified as risk factors for breast cancer. Breast cancer is the second leading cause of death among women.

Different chemotherapeutic agents are known in the art for treating breast cancer. Cytoxic agents used for treating breast cancer include doxorubicin,cyclophosphamide, methotrexate, 5-fluorouracil, mitomycin C, mitoxantrone, taxol, and epirubicin. (CANCER SURVEYS, Breast Cancer volume 18, Cold Spring Harbor Laboratory Press, 1993).

In the treatment of locally advanced noninflammatory breast cancer, a matrix metalloproteinase inhibitor and radiation therapy can be used to treat the disease in combination with other antiangiogenic agents, or in combination with surgery, or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, and surgery that can be used in combination with the radiation therapy and MMP inhibitors include, but are not limited to: 1) doxorubicin, vincristine; 2) cyclophosphamide,

doxorubicin, 5-flourouracil, vincristine, prednisone; 3) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen; 4) cyclophosphamide, doxorubicin, 5-flourouracil, premarin, tamoxifen, mastectomy; 5) mastectomy, levamisole; 6) mastectomy; and 7) mastecomy, cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen, halotestin.

In the treatment of locally advanced inflammatory breast cancer, MMP inhibitors and radiation therapy can be used to treat the disease in combination with other antiangiogenic agents, or in combination with surgery, or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, radiation therapy and surgery that can be used in combination with the MMP inhibitors and radiation include, but or not limited to: 1) cyclophosphamide, doxorubicin, 5-fluorouracil; 2) cyclophosphamide, doxorubicin, 5-fluorouracil, mastectomy; 3) 5-flurouracil, doxorubicin, clyclophosphamide, vincristine, prednisone, mastectomy; 4) 5-flurouracil, doxorubicin, clyclophosphamide, vincristine, mastectomy; 5) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine; 6) cyclophosphamide, doxorubicin, 5-fluorouracil, vincristine, mastectomy; 7) doxorubicin, vincristine, methotrexate, followed by vincristine, cyclophosphamide, 5-florouracil; 8) doxorubicin, vincristine, cyclophosphamide, methotrexate, 5-florouracil, followed by vincristine, cyclophosphamide, 5-florouracil; 9) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 10) surgery, followed by cyclophosphamide,

methotrexate, 5-fluorouracil, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 11) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine, tamoxifen;; 12) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine; 13) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine, tamoxifen; 14) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, doxorubicin, vincristine; 15) surgery, followed by cyclophosphamide, methotrexate, 5-fluorouracil, predinsone, tamoxifen, followed by cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, vincristine; 16) 5-florouracil, doxorubicin, cyclophosphamide followed by mastectomy, followed by 5-florouracil, doxorubicin, cyclophosphamide.

In the treatment of metastatic breast cancer, radiation therapy and MMP inhibitors are used to treat the disease in combination with surgery, or with chemotherapeutic agents. Preferred combinations of chemotherapeutic agents, and surgery that can be used in combination with the radiation therapy and MMP inhibitors include, but are not limited to: 1) cyclosphosphamide, methotrexate, 5-fluorouracil; 2)

cyclophosphamide, adriamycin, 5-fluorouracil; 3) cyclosphosphamide, methotrexate, 5-flurouracil, vincristine, prednisone; 4) adriamycin, vincristine; 5) thiotepa, adriamycin, vinblastine; 6) mitomycin, vinblastine; 7) cisplatin, etoposide.

Bladder Cancer

The classification of bladder cancer is divided into three main classes: 1) superficial disease, 2) muscle-invasive disease; and 3) metastatic disease.

Currently, transurethral resection (TUR), or segmental resection, account for first line therapy of superficial bladder cancer, i.e., disease confined to the mucosa or the lamina propria. However, intravesical therapies are necessary, for example, for the treatment of high-grade tumors, carcinoma in situ, incomplete resections, recurrences, and multifocal papillary. Recurrence rates range from up to 30 to 80 percent, depending on stage of cancer.

Therapies that are currently used as intravesical therapies include chemotherapy, immuontherapy, bacille Calmette-Guerin (BCG) and photodynamic therapy. The main objective of intravesical therapy is twofold: to prevent recurrence in high-risk patients and to treat disease that cannot by resected. The use of intravesical therapies must be balanced with its potentially toxic side effects. Additionally, BCG requires an unimpaired immune system to induce an antitumor effect. Chemotherapeutic agents that are known to be inactive against superficial bladder cancer include Cisplatin, actinomycin D, 5-fluorouracil, bleomycin, and cyclophosphamide methotrxate.

In the treatment of superficial bladder cancer, MMP inhibitors and radiation therapy are used to treat the

disease in combination with surgery (TUR), and intravesical therapies.

Preferred combinations of chemotherapeutic agents are selected from the group consisting of thiotepa (30 to 60 mg/day), mitomycin C (20 to 60 mg/day), and doxorubicin (20 to 80 mg/day).

The preferred intravesicle immunotherapuetic agent that may be used in the present invention is BCG. The preferred daily dose ranges from 60 to 120 mg, depending on the strain of the live attenuated tuberculosis organism used.

The preferred photodynamic therapuetic agent that may be used with the present invention is Photofrin I, a photosensitizing agent, administered intravenously. It is taken up by the low-density lipoprotein receptors of the tumor cells and is activated by exposure to visible light. Additionally, neomydium YAG laser activation generates large amounts of cytotoxic free radicals and singlet oxygen.

In the treatment of muscle-invasive bladder cancer, radiation therapy and MMP inhibitors can be used to treat the disease in combination with other antiangiogenic agents, or in combination with surgery (TUR), intravesical chemotherapy, and radical cystectomy with pelvic lymph node dissection.

The preferred radiation dose is between 5,000 to 7,000 cGY in fractions of 180 to 200 cGY to the tumor. Additionally, 3,500 to 4,700 cGY total dose is administered to the normal bladder and pelvic contents in a four-field technique. Radiation therapy should be considered only if the patient is not a surgical candidate, but may be considered as preoperative therapy.

The preferred combination of chemotherapeutic agents that can be used in combination with radiation therapy and the MMP inhibitors is cisplatin, methotrexate, vinblastine.

Currently no curative therapy exists for metastatic bladder cancer. The present invention contemplates an effective treatment of bladder cancer leading to improved tumor inhibition or regression, as compared to current therapies.

In the treatment of metastatic bladder cancer, a combination of radiation therapy and MMP inhibitors can be used to treat the disease in combination with surgery, or with chemotherapeutic agents.

Preferred combinations of chemotherapeutic agents include, but are not limited to: 1) cisplatin and methotrexate; 2) doxorubicin, vinblastine, cyclophoshamide, and 5-fluorouracil; 3) vinblastine, doxorubicin, cisplatin, methotrexate; 4) vinblastine, cisplatin, methotrexate; 5) cyclophosphamide, doxorubicin, cisplatin; 6) 5-fluorouracil, cisplatin.

Head and Neck Cancers

Head and neck cancer accounts for approximately 2% of new cancer cases in the United States. Common intracranial neoplasms include glioma, meningioma, neurinoma, and adenoma. Preferred combinations that can be used along with a combination of radiation therapy and an integrin antagonist for the treatment of malignant glioma include: 1) BCNU (carmustine); 2) methyl CCNU (lomustine); 3) medrol; 4) procarbazine; 5) BCNU, medrol; 6) misonidazole, BCNU; 7) streptozotocin; 8) BCNU, procarbazine; 9) BCNU, hydroxyurea, procarbazine, VM-26; 10) BNCU, 5-flourouacil; 11) methyl CCNU, dacarbazine;

12) misonidazole, BCNU; and 13) PCNU. The preferred dose of radiation therapy is about 5,500 to about 6,000 cGY. Preferred radiosensitizers include misonidazole, intra-arterial Budr and intravenous iododeoxyuridine (IUdR).

Biological Evaluation

Solitary tumors are generated in the right hind legs of mice by the injection of 3 x 10^5 viable NFSA tumor cells. Treatment with a MMP inhibitor (6 mg/kg body weight) or vehicle (0.05% Tween 20 and 0.95% polyethylene glycol) given in the drinking water is started when tumors are approximately 6 mm in diameter and the treatment is continued for 10 consecutive days. Water bottles are changed every 3 days. Tumor irradiation is performed 3-8 days after initiation of the treatment with a MMP inhibitor. The end points of the treatment are tumor growth delay (days) and TCD_{50} (tumor control dose 50, defined as the radiation dose yielding local tumor cure in 50% of irradiated mice 120 days after irradiation). To obtain tumor growth curves, three mutually orthogonal diameters of tumors are measured daily with a vernier caliper, and the mean values are calculated.

Local tumor irradiation with single γ-ray doses of 30, 40, or 50 Gy is given when these tumors reach 8 mm in diameter. Irradiation to the tumor is delivered from a dual-source ^{137}Cs irradiator at a dose rate of 6.31 Gy/minute. During irradiation, unanesthetized mice are immobolized on a jig and the tumor is centered in a circular radiation field 3 cm in diameter. Regression and regrowth of tumors are followed at 1-3 day intervals until the tumor diameter reaches approximately 14 mm.

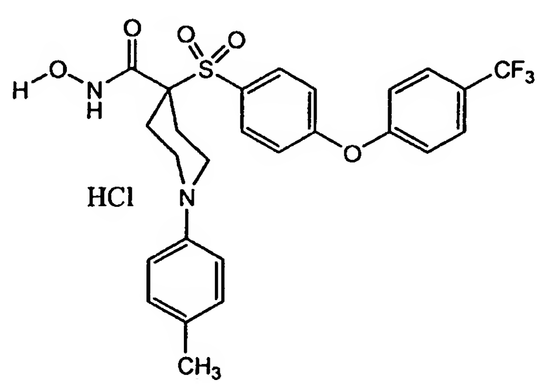
What is claimed is:

1. A method for treating neoplasia in a mammal in need of such treatment, comprising treating said mammal with radiation therapy and a therapeutically effective amount of a matrix metalloproteinase inhibitor or pharmaceutically-acceptable salt thereof.

2. The method of Claim 1 wherein the neoplasia is selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

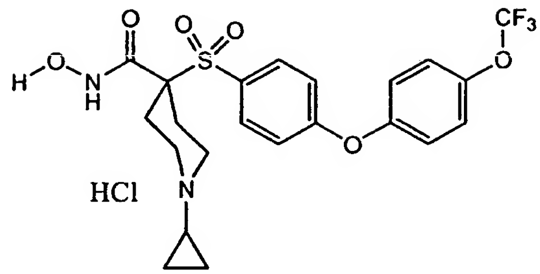
3. A method for treating neoplasia in a subject in need of such treatment, comprising treating said mammal with radiation therapy and a therapeutically effective amount of a matrix metalloproteinase inhibitor or pharmaceutically-acceptable salt thereof, wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of

1)



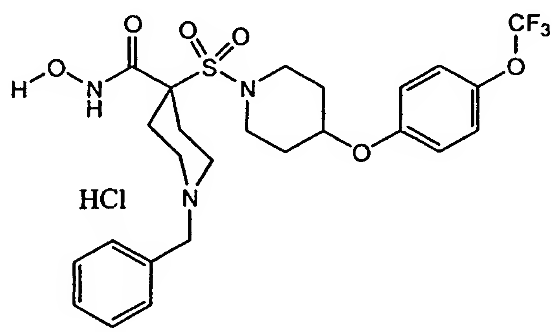
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

2)



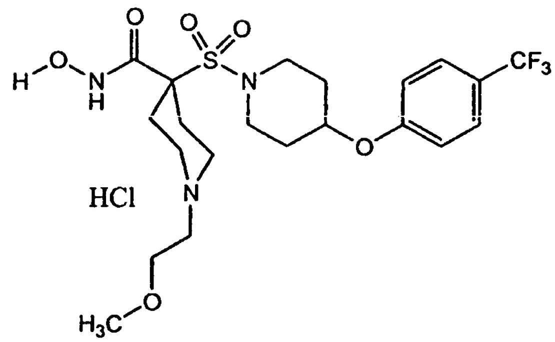
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

3)



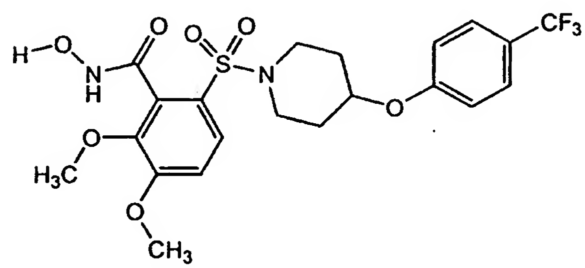
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

4)



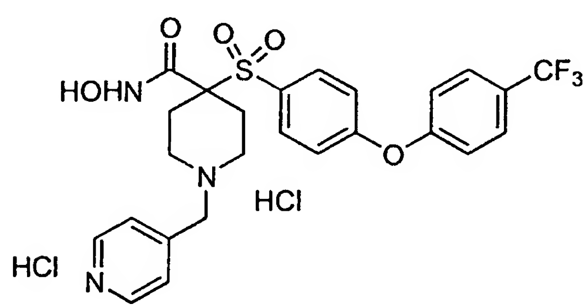
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

5)



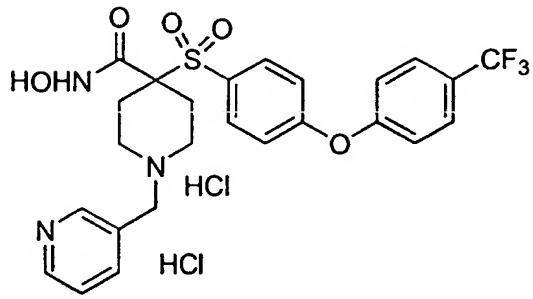
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide;

6)



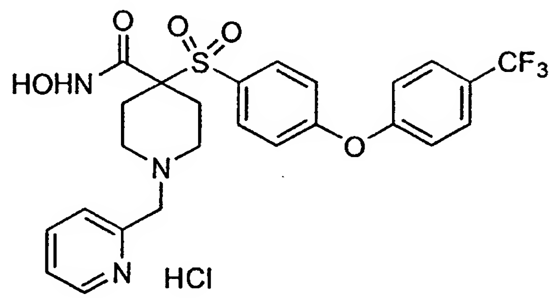
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

7)



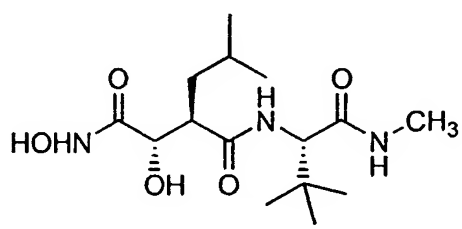
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

8)



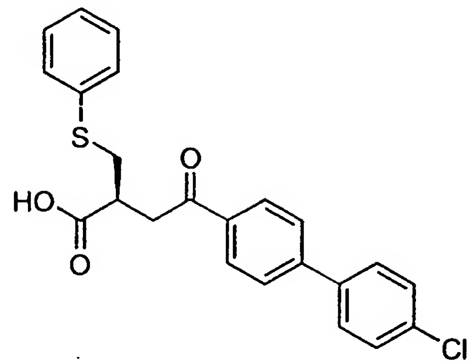
N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

9)



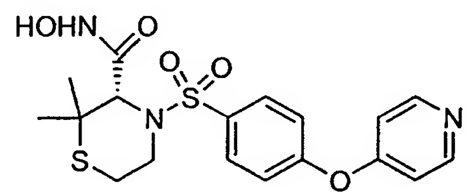
British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-);

10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid;

11)

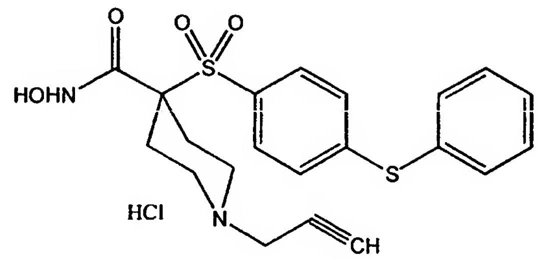


Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2- dimethyl- 4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]- 3-thiomorpholinecarboxamide;

12) CollaGenex Pharmaceuticals CMT-3 (Metastat), 6- demethyl-6-deoxy-4-dedimethylaminotetracycline;

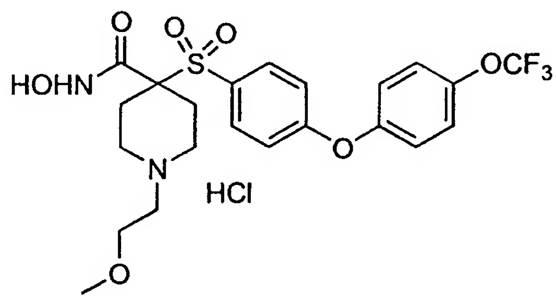
13) Chiroscience D-2163, 2- [1S- ([(2R,S)-acetylmercapto- 5- phthalimido]pentanoyl- L-leucyl)amino- 3- methylbutyl]imidazole;

14)



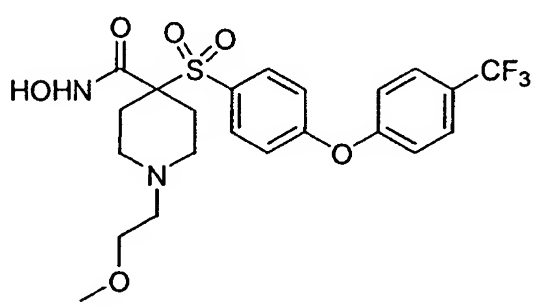
N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride;

15)



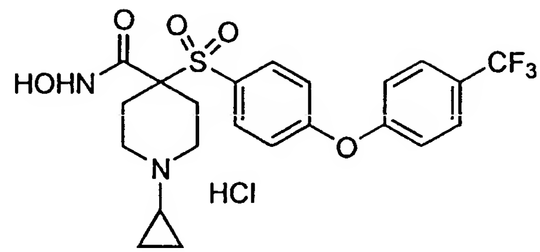
N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4 (trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

16)



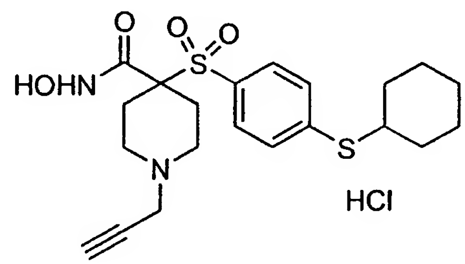
N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinearboxamide;

17)



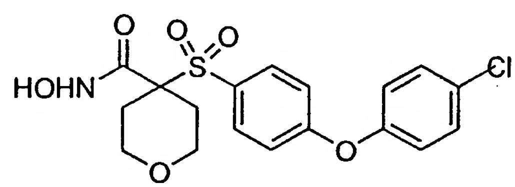
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

18)



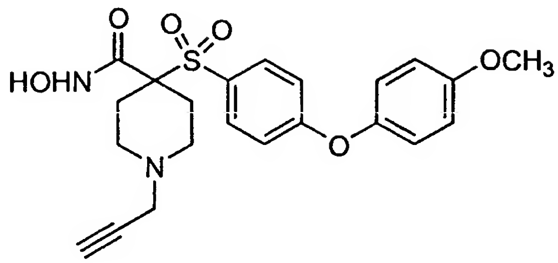
4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride;

19)



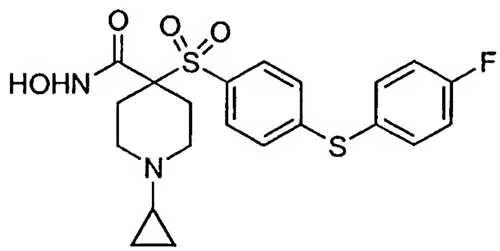
4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide;

20)



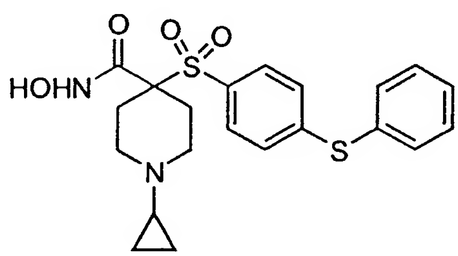
N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl)sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide;

21)



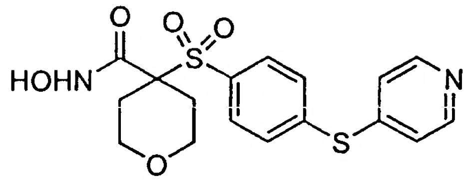
1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide;

22)



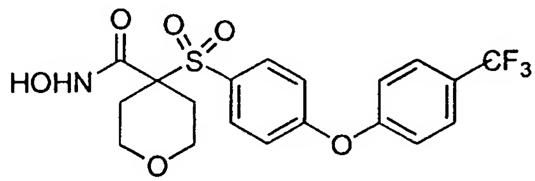
1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide;

23)



tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide;

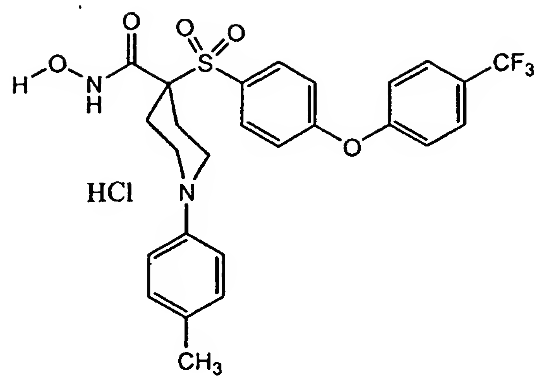
24)



tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide.

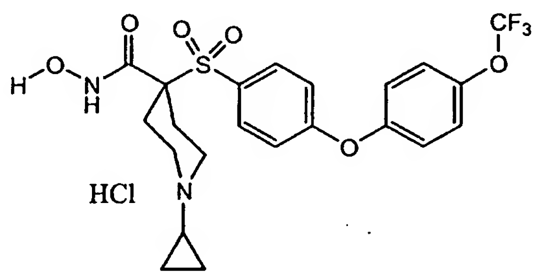
4. A method for treating neoplasia in a mammal in need of such treatment, comprising treating said mammal with radiation therapy and a therapeutically effective amount of a matrix metalloproteinase inhibitor or pharmaceutically-acceptable salt thereof, wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of

1)



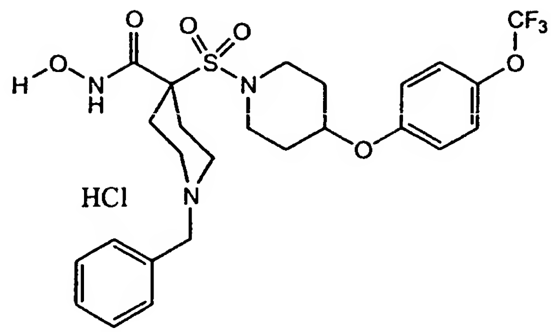
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

2)



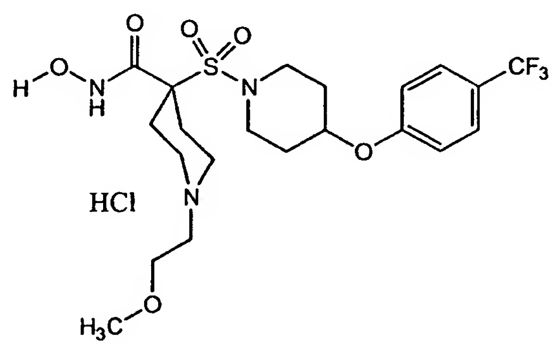
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

3)



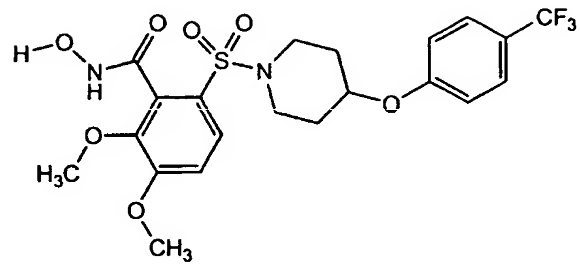
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

4)



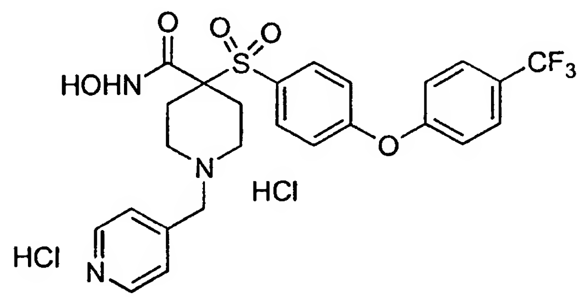
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

5)



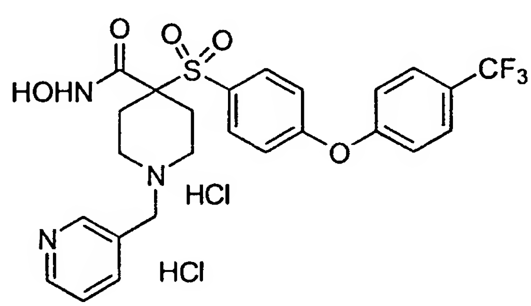
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide;

6)



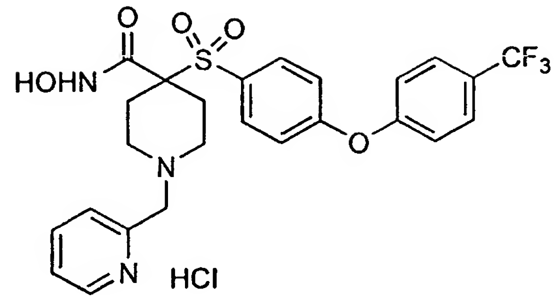
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

7)



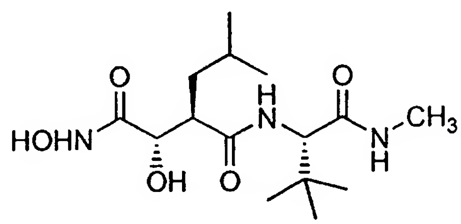
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride;

8)



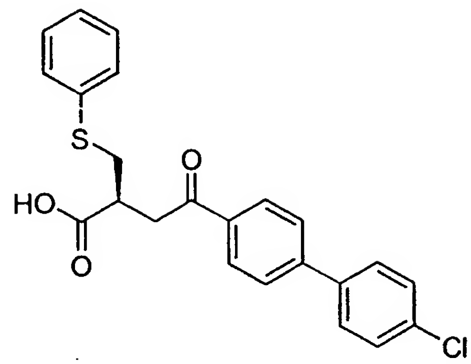
N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride;

9)



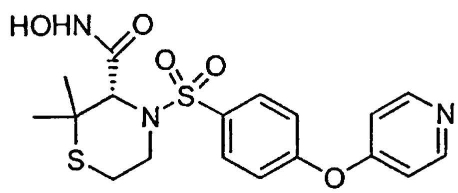
British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]- N1,2 -dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-);

10)



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid;

11)

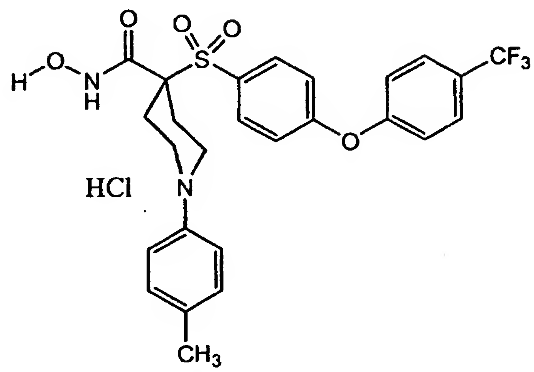


Agouron Pharmaceuticals AG-3340, N-hydroxy- 2,2- dimethyl- 4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]- 3-thiomorpholinecarboxamide;

12) CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline; and

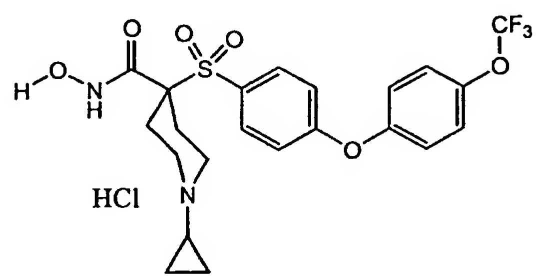
13) Chiroscience D-2163, 2- [1S- ([(2R,S)-acetylmercapto- 5- phthalimido]pentanoyl- L-leucyl)amino- 3- methylbutyl]imidazole.

5. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



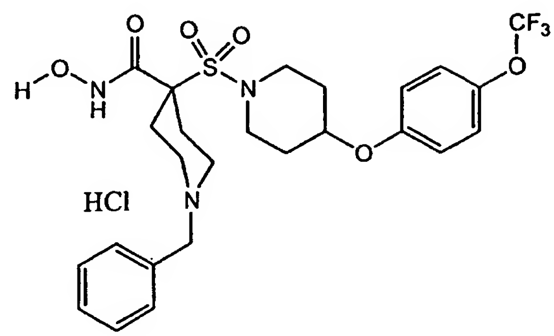
N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

6. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



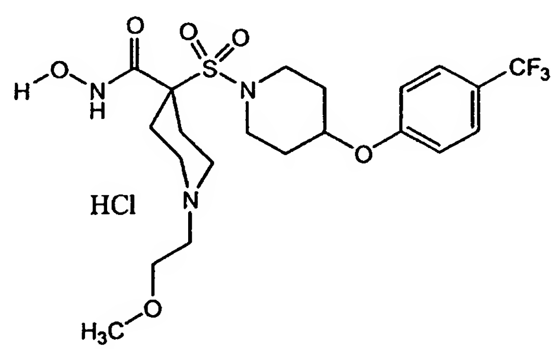
1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

7. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



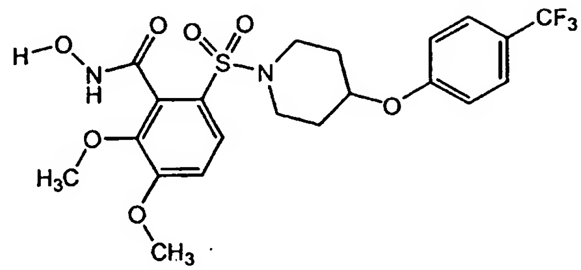
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

8. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



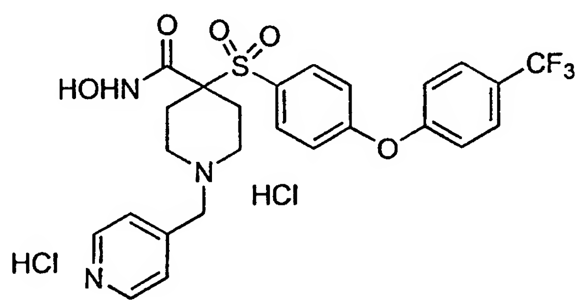
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

9. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



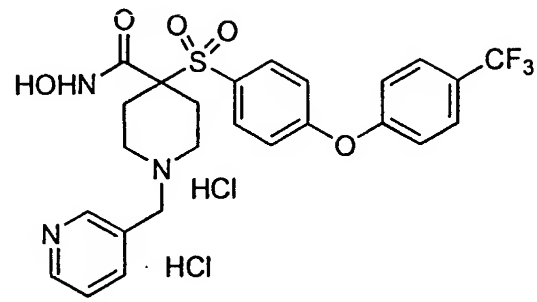
N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

10. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



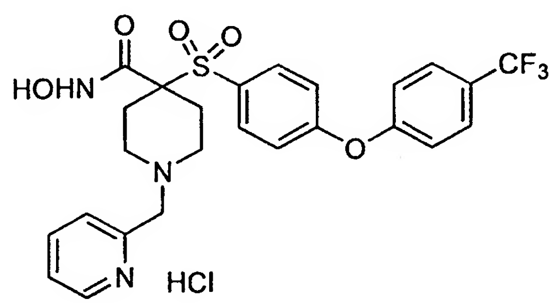
N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

11. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



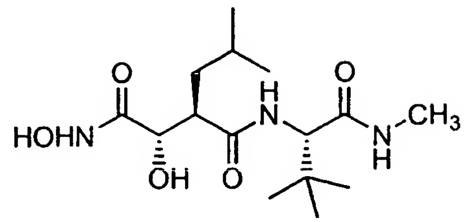
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

12. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



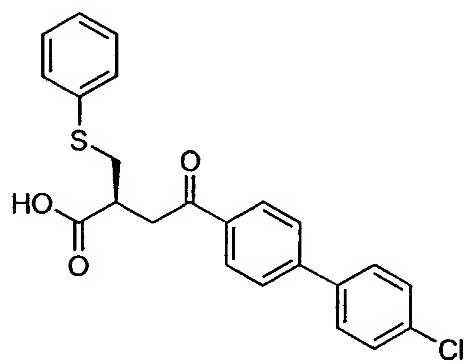
N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

13. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



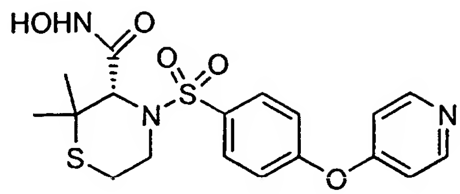
British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl- 1-[(methylamino)carbonyl]propyl]-N1,2 - dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R*),2R*,3S*]]-).

14. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]- 4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid.

15. The method of claim 3 wherein the matrix metalloproteinase inhibitor is



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2- dimethyl- 4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]- 3-thiomorpholinecarboxamide.

16. The method of claim 3 wherein the matrix metalloproteinase inhibitor is CollaGenex Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-dedimethylaminotetracycline.

17. The method of claim 3 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-[1S- ([(2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-L- leucyl)amino- 3- methylbutyl]imidazole.

18. A combination comprising radiation therapy and a therapeutically effective amount of a matrix metalloproteinase inhibitor or pharmaceutically-acceptable salt thereof.

19. The method of Claim 1 wherein the combination is administered in a sequential manner.

20. The method of Claim 1 wherein the combination is administered in a substantially simultaneous manner.

21. The method of Claim 3 wherein the combination is administered in a sequential manner.

22. The method of Claim 3 wherein the combination is administered in a substantially simultaneous manner.